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Enhancement of whole body glucose uptake during and after human skeletal muscle low-frequency electrical stimulation

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Hamada, Taku, Hideki Sasaki, Tatsuya Hayashi, Toshio Moritani, and Kazuwa Nakao. Enhancement of whole body glucose uptake during and after human skeletal muscle low-frequency electrical stimulation. *J Appl Physiol* 94: 2107–2112, 2003. First published January 31, 2003; 10.1152/japphysiol.00486.2002.—There is considerable evidence to suggest that electrical stimulation (ES) activates glucose uptake in rodent skeletal muscle. It is, however, unknown whether ES can lead to similar metabolic enhancement in humans. We employed low-frequency ES through surface electrodes placed over motor points of quadriceps femoris muscles. In male subjects lying in the supine position, the highest oxygen uptake was obtained by a stimulation pattern with 0.2-ms biphasic square pulses at 20 Hz and a 1-s on-off duty cycle. Oxygen uptake was increased by approximately twofold throughout the 20-min stimulation period and returned to baseline immediately after stimulation. Concurrent elevation of the respiratory exchange ratio and blood lactate concentration indicated anaerobic glycogen breakdown and utilization during ES. Whole body glucose uptake determined by the glucose disposal rate during euglycemic clamp was acutely increased by $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in response to ES and, moreover, remained elevated by $3\text{--}4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for at least 90 min after cessation of stimulation. Thus the stimulatory effect of ES on whole body glucose uptake persisted not only during, but also after, stimulation. Low-frequency ES may become a useful therapeutic approach to activate energy and glucose metabolism in humans.

glucose transport; euglycemic clamp; exercise; insulin sensitivity; oxygen uptake

PHYSICAL EXERCISE HAS PROFOUND effects on energy and fuel metabolism in contracting skeletal muscle. It is well established that exercise can directly activate glucose uptake in skeletal muscle by inducing translocation of GLUT-4 glucose transporters to the cell surface via an insulin-independent mechanism (contraction-stimulated glucose transport) (10, 11, 31, 37, 49). This phenomenon is considered responsible for the acute effect of exercise on glucose transport, with the majority of glucose being taken up by contracting skeletal muscle.

In fact, contraction-stimulated GLUT-4 translocation is not impaired in insulin-resistant conditions such as Type 2 diabetes and obesity (25). Furthermore, the period after exercise is also characterized by a substantial increase in insulin sensitivity that leads to insulin-dependent GLUT-4 translocation and glucose transport as a local phenomenon restricted to exercised muscles (9, 13, 39, 40, 48a). Thus these insulin-independent and -dependent mechanisms of exercise have been widely utilized to prevent individuals from developing glucose intolerance and to improve glycemic control in patients with Type 2 diabetes.

Clinically, electrical stimulation (ES) of muscle is useful as a modality of assisting muscle contraction for those who have difficulties in performing voluntary exercise. The use of ES has been traditionally employed for muscle strengthening, maintenance of muscle mass and strength, and restoring neuromuscular functions after stroke or spinal cord injury (28). ES can also cause cardiorespiratory activation (4, 7, 20, 44). Furthermore, there is substantial evidence concerning the effects of ES on metabolic responses and fuel utilization in skeletal muscle (12, 19, 26, 27, 44). Although a number of animal studies, most of which used rat skeletal muscles, have shown that a single bout of ES can activate both insulin-independent (11, 31, 37, 49) and -dependent glucose uptake (9, 40), it has not been examined whether similar metabolic effects can be achieved by ES of human skeletal muscle.

The present study was, therefore, undertaken to examine whether involuntary muscle contraction induced by percutaneous muscle stimulation causes acute enhancement of glucose uptake in human subjects. To our knowledge, this is the first report demonstrating that ES, with appropriate stimulation parameters, can activate whole body glucose uptake, not only during the stimulation period but also after cessation of ES under the condition of physiological hyperinsulinemia.

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METHODS

Subjects. Informed consent was obtained from 14 male graduate students after a detailed explanation of experimental procedures and associated risks. All subjects were instructed to refrain from consuming caffeine or engaging in strenuous exercise for 48 h before each experiment. None of the subjects had prior engagement in regular resistance or endurance training programs and were free of metabolic, neuromuscular, cardiovascular disorders, and recent illness. The study protocol was approved by the Ethical Committee of Kyoto University Graduate School.

Determination of stimulation parameters. Stimulation parameters used in previous studies were quite diverse, and physiological responses were difficult to compare (1, 12, 19, 26, 27, 44). Therefore, we first determined the optimal ES parameters that induced the highest oxygen uptake during 20 min of ES of both quadriceps muscles. In six subjects (age 24.0 ± 0.8 yr, height 178.0 ± 2.4 cm, weight 68.5 ± 2.6 kg), we tested the effects of various ES parameters, including frequency, polarity (monophasic vs. biphasic), and stimulation-rest duty cycle. Subjects were required a maximum of four visits to the laboratory. Testing was separated by at least 1 wk and randomized among subjects.

After reporting to the laboratory, each subject sat resting for 20 min. Subjects were then asked to lie in the supine position, with the lower legs flexed over the end of the bed. The right leg was secured to a strain gauge by a strap around the ankle. Two rubber stimulation surface electrodes (6.5×8.5 cm) were placed over motor points in the proximal and midportion of each quadriceps muscle. Before application of stimulation electrodes, the skin surface was prepared by shaving, sanding, and applying isopropyl alcohol. Five minutes after all of the settings were adjusted, oxygen uptake and knee extension force measurements were initiated. Our laboratory's method for measuring oxygen uptake has been described in previous communications (34, 36). Respiratory gas parameters were continuously monitored throughout a total period of 35 min, including pre- (5 min), during (20 min), and poststimulation (10 min) periods. Subjects breathed through a low-resistance valve, and the expired gas was sampled from a mixing chamber in synchrony with the breath cycle. Analog signals of fractional concentrations of O_2 and CO_2 and flow rate from an AE 280 analyzer (Minato Medical Science, Tokyo, Japan) were continuously digitized at a sampling rate of 50 Hz by a 13-bit analog-to-digital converter. For force recordings, signals from the strain gauge were amplified and digitized at a sampling rate of 1 kHz and stored on a hard disk for subsequent measurements. Electrical square pulses of 0.2-ms duration were then delivered from an electrical stimulator (Omron, Kyoto, Japan). Stimulator output voltage was limited to 80 V for nonpainful muscle stimulation. Blood lactate concentrations were determined by the lactate oxidase method by using an automated analyzer (Lactate Pro; Arklay, Kyoto, Japan).

Glucose uptake measurement. For the second experiment, eight subjects (age 23.4 ± 0.6 yr, height 171.1 ± 2.6 cm, weight 61.0 ± 2.6 kg) were tested for a measurement of glucose uptake by using a hyperinsulinemic-euglycemic clamp, according to the method by DeFronzo et al. (6), with the aid of a blood glucose monitoring and glucose-insulin infusion system (Artificial Pancreas model STG22; Nikkiso, Tokyo, Japan) (22, 45). After an overnight fast, subjects arrived at a clinical research room in Kyoto University Hospital at 8:30 AM and were kept in the supine position with both knees extended. Surface electrodes were placed over each quadriceps muscle. A polyethylene catheter was placed

in a right antecubital vein and connected to the artificial pancreas for continuous monitoring of blood glucose by using the glucose oxidase method. A second catheter was inserted into a left antecubital vein for continuous infusion of insulin and glucose. After collection of a baseline blood sample for insulin measurement, insulin infusion was primed with Humulin R (Eli Lilly, Indianapolis, IN) for 10 min (0–1 min, 3.56; 1–2 min, 3.17; 2–3 min, 2.82; 3–4 min, 2.52; 4–5 min, 2.24; 5–6 min, 1.99; 6–7 min, 1.77; 7–8 min, 1.58; 8–9 min, 1.41; 9–10 min, $1.25 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) followed by constant insulin infusion at $1.12 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Priming of glucose infusion with the use of a 20% glucose solution was also performed (4–10 min, 2.0; 10–15 min, 2.5; 15–16 min, 4.0 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and, thereafter, baseline plasma glucose level was maintained by adjusting the glucose infusion rate. At least 90 min after starting insulin infusion, simultaneous isometric contractions of both quadriceps muscles were produced for a period of 20 min. Additional blood samples were obtained at the beginning and the end of the ES period and then every 30 min after ES. Glucose disposal rate (GDR) was expressed as milligrams of glucose infused per kilogram body weight per minute. Serum insulin concentrations were determined by enzyme immunoassay (Eiken Chemical, Tokyo, Japan).

Statistical analysis. Data are expressed as means \pm SE. Oxygen uptake and force generation under various stimulation parameters were analyzed by two-way ANOVA. A one-way ANOVA was used to test whether respiratory gas parameters, force generation, blood lactate, and glucose disposal changed over the time course, with a subsequent Tukey's post hoc test. The probability level accepted for statistical significance was $P < 0.05$.

RESULTS

In regards to the stimulation parameters, it was found that a stimulation frequency either lower (10 Hz) or higher (60 Hz) than 20 Hz, with a 1-s on-off duty cycle, resulted in lower oxygen uptake and accumulated force generation, although the differences were not statistically significant. In addition, biphasic polarity tended to result in greater oxygen uptake compared with monophasic polarity. An on-off duty cycle of either 1 or 2 s did not differentially affect oxygen uptake and force generation. Interestingly, it was found that stimulation at 60 Hz with an identical electrical intensity and polarity pattern resulted in marked loss of force toward the end of stimulation, possibly due to impaired neuromuscular transmission or membrane excitation, i.e., high-frequency fatigue (35). We, therefore, adopted a stimulation pattern with a frequency of 20 Hz, a 1-s on-off duty cycle, and biphasic polarity as the optimal condition for ES and used this in the subsequent studies.

Figure 1A is a time course of the changes in oxygen uptake while resting, during 20 min of muscle stimulation, and in the subsequent 5-min resting period. Oxygen uptake was rapidly increased by approximately twofold with the onset of ES, remained fairly constant throughout ES, and then returned to the prestimulation level immediately after stopping ES. Mean oxygen uptake during ES was significantly higher than that of the prestimulation period (3.2 ± 0.1 vs. $5.7 \pm 0.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P < 0.01$) (Fig. 1B). Mean

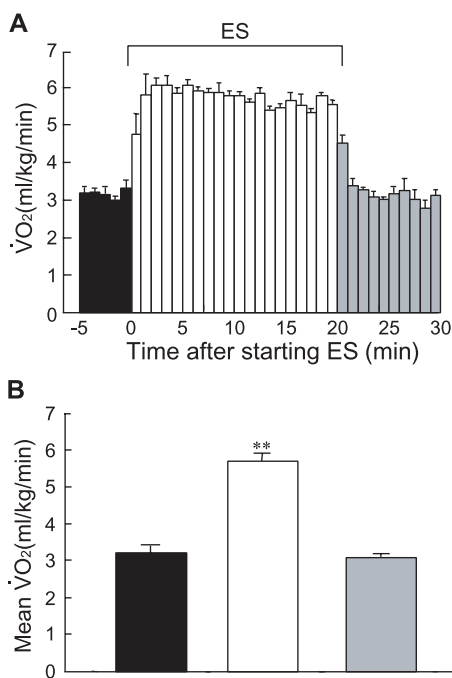


Fig. 1. A: time course of changes in whole body oxygen uptake ($\dot{V}O_2$). $\dot{V}O_2$ was continuously monitored by respiratory gas exchange analysis before (solid bars), during (open bars), and after (shaded bars) electrical stimulation (ES) of quadriceps femoris muscles with 0.2-ms biphasic pulses at 20 Hz with a 1-s on-off duty cycle. B: mean $\dot{V}O_2$ before (solid bar), during (open bar), and after (shaded bar) ES. Values are means \pm SE; $n = 6$. ** $P < 0.01$ vs. baseline (before ES).

isometric force generation during ES declined to $71 \pm 3\%$ after 5 min of ES and $49 \pm 3\%$ at the end of stimulation compared with the mean force generated during the first minute (Fig. 2). The respiratory gas exchange ratio (Fig. 3A) and blood lactate concentration (Fig. 3B) were elevated at the initial phase of ES and then gradually decreased toward the end of ES.

Whole body glucose disposal was assessed by the amount of glucose required to maintain fasting plasma glucose during clamp. Similar to the elevation of oxygen uptake, GDR was acutely increased in response to

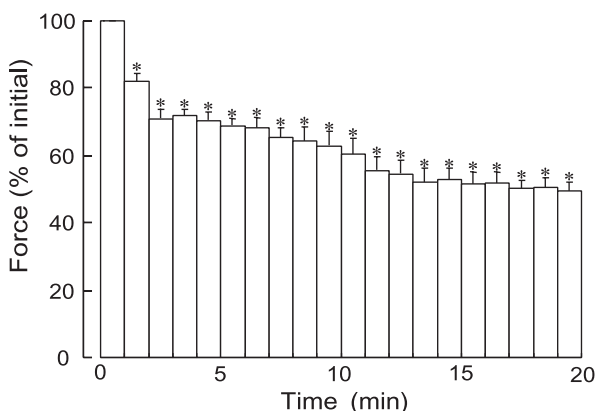


Fig. 2. Time course of changes in force generation during ES of quadriceps femoris muscles with 0.2-ms biphasic pulses at 20 Hz with a 1-s on-off duty cycle. Values are means \pm SE of the percentage of the first-minute value; $n = 6$. * $P < 0.05$ vs. baseline (before ES).

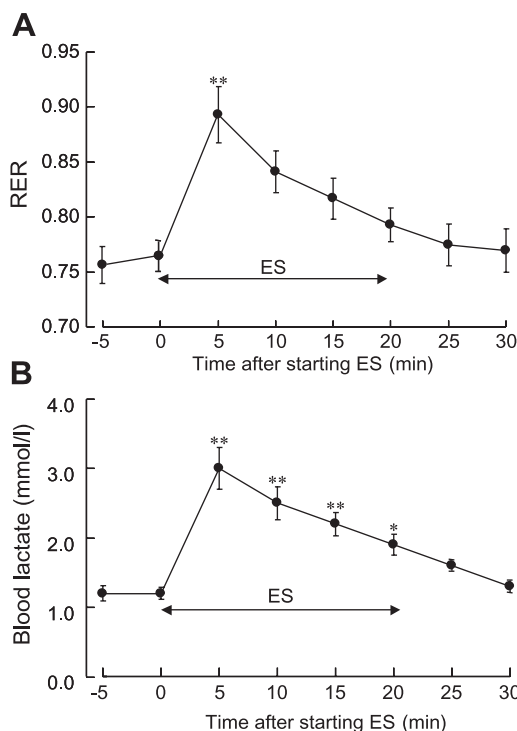


Fig. 3. Time course of changes in respiratory gas exchange ratios (RER; A) and blood lactate concentrations (B) during ES of quadriceps femoris muscles with 0.2-ms biphasic pulses at 20 Hz with a 1-s on-off duty cycle. Values are means \pm SE; $n = 6$. * $P < 0.05$ and ** $P < 0.01$ vs. baseline (0 min).

ES and remained increased for at least 90 min after the cessation of ES (Fig. 4). The mean increase in GDR above prestimulation was $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during stimulation ($P < 0.01$), and there was an even greater requirement for glucose during the poststimulation period (20–50 min, $2.9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; 50–80 min, $2.9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; 80–110 min, $4.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ above prestimulation) (Table 1). Because it has been shown that skeletal muscle is the principal tissue for whole body glucose disposal under hyperinsulinemic conditions (6), these findings clearly indicate the acute stimulatory effect of ES on glucose uptake in skeletal muscle. The stability of the plasma glucose concentration during clamp was quite satisfactory, i.e., the coefficient of variation was found to be 3.0%. Insulin concentration during clamp was constant and within the range of physiological hyperinsulinemia that was sufficient to suppress endogenous glucose production (41) (Table 1).

DISCUSSION

Regular physical exercise results in numerous health benefits, including a reduced risk of developing Type 2 diabetes. However, there are individuals who are restricted from voluntary physical activity and in a bedridden state due to chronic illness, spinal cord injury, or other forms of disability. Lipman et al. (29, 30) have shown that a chronic lack of physical activity is associated with reduced peripheral glucose uptake due to insulin resistance. More recently, Mikines et al. (32)

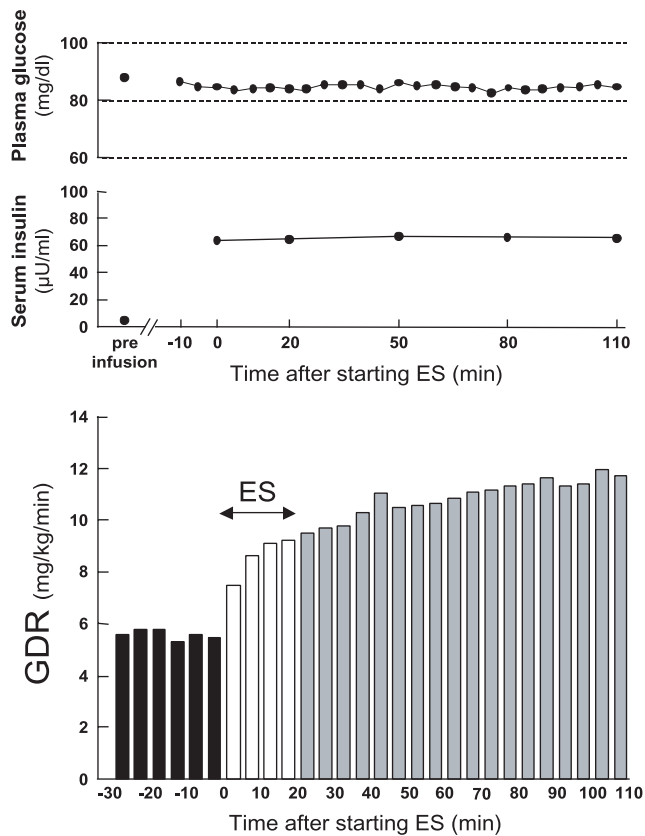


Fig. 4. Representative time courses of changes in plasma glucose, serum insulin, and glucose disposal rate (GDR) during euglycemic clamp. Glucose and insulin concentrations and mean GDR were determined every 5 min before (solid bars), during (open bars), and after (shaded bars) ES.

and Stuart et al. (47) have demonstrated that physical inactivity caused by bed rest for as little as 7 days is associated with a substantial reduction in insulin sensitivity in inactive skeletal muscle without changing the effect of insulin on hepatic glucose production. In addition, prolonged physical inactivity has been shown to decrease the oxygen transport capacity of skeletal muscle (43) and also result in decreased muscle GLUT-4 content associated with insulin resistance (48). Although ES-assisted training is effective for increasing glucose transporters and improving insulin sensitivity in patients with spinal cord injury (3, 33), the effects of a single bout of ES on glucose uptake have never been studied in humans. The novel and, moreover, clinically important finding of the present study is that whole body glucose uptake is acutely increased

in response to 20 min of ES, and this increase lasts for at least 90 min after the cessation of ES under physiological hyperinsulinemia (~70 µU/ml). It is also notable that the postexercise increase in GDR is as high as that seen by bicycle exercise (40% of maximal oxygen uptake, 30 min) performed under similar hyperinsulinemia (~77 µU/ml) (5).

Exercise can increase the rate of muscle glucose uptake via two distinct mechanisms, i.e., an insulin-independent one (contraction-stimulated glucose uptake) and an insulin-dependent one (postexercise increase in insulin sensitivity). Wallberg-Henriksson (48a) have shown, in isolated rat skeletal muscle, that the activity of insulin-independent glucose uptake is maximally enhanced immediately after exercise and then gradually wears off, but ~34% of the initial activity is still present at 180 min. In contrast, increased insulin sensitivity is undetectable in the early phase of the postexercise period (at 30 and 60 min) and becomes prominent at 180 min after exercise (48a). Consistent with these findings, Price et al. (38) have shown in human muscle that postexercise glycogen repletion occurs in an insulin-independent manner for ~1 h after exercise, and thereafter insulin-dependent glycogen repletion becomes significant. Thus it appears that the increase in GDR after ES found in this study is likely due, at least in a large part, to the insulin-independent effect of muscle contraction, and the insulin-dependent effect may come into play particularly during the latter part of the poststimulation period.

The concurrent elevation of the respiratory exchange ratio and blood lactate concentration after the onset of ES indicates anaerobic breakdown and utilization of intramuscular glycogen in contracting muscle. In fact, Hultman and Spriet (19) have shown that ES for 45 min at 20 Hz causes a 44% decrease in glycogen concentration in quadriceps muscle, and Kim et al. (26) have also found a significant decrease in glycogen content using ES for 60 min at 50 Hz. Unlike the orderly recruitment of motor units during voluntary contraction, motor units for type II fibers are more active due to larger axonal diameter with lower electrical resistance against external ES (16). Thus ES can result in preferential activation of type II fibers that have a larger capacity for glycogen utilization in humans (46). In addition, rates of glycogenolysis during ES are two-fold higher in type II fibers than type I fibers (12). To our knowledge, there have been no studies in humans designed to investigate a possible relationship between fiber type and glucose transport during ES, but studies

Table 1. Plasma glucose, serum insulin, and glucose disposal rate during euglycemic clamp

	Preinfusion	Pre-ES -30-0 min	During ES 0-20 min	Post-ES 20-50 min	Post-ES 50-80 min	Post-ES 80-110 min
Plasma glucose, mg/dl	85.0 ± 1.0	81.8 ± 0.6	78.6 ± 1.0	83.5 ± 1.1	79.6 ± 0.5	79.4 ± 0.4
Serum insulin, µU/ml	4.1 ± 0.5	65.7 ± 3.6	69.3 ± 5.7	70.6 ± 5.3	73.1 ± 5.1	70.1 ± 4.5
GDR, mg·kg ⁻¹ ·min ⁻¹		7.2 ± 0.4	9.7 ± 0.9*	10.1 ± 0.6*	10.1 ± 0.4*	11.4 ± 0.8*

Values are means ± SE (n = 8). Plasma glucose and glucose disposal rate (GDR) were determined continuously, and mean values of the indicated time periods are shown. ES, electrical stimulation. Serum insulin was determined at the end of the indicated time period. *P < 0.01 vs. pre-ES.

in rat have shown that glucose transport activity can be higher in type II than type I fibers when ES is employed (21, 42).

Although increased glucose uptake is not necessarily associated with glycogen depletion (8, 15), glycogen content seems to be closely related to both insulin-independent and -dependent glucose uptake in skeletal muscle. Recent studies have revealed that 5'-AMP-activated protein kinase (AMPK) is a signaling intermediary leading to insulin-independent glucose uptake (14, 15). AMPK is activated in response to an increase in the AMP-to-ATP ratio in muscle cells, indicating its role as an energy sensor in muscle cells. AMPK is stimulated by various glycogen-depleting stimuli, such as contraction, hypoxia, hyperosmolarity, and pharmacological inhibition of oxidative phosphorylation, with a close correlation to glucose transport activity in rat skeletal muscle (14). In fact, contraction-induced activation of AMPK and GLUT-4 translocation-glucose uptake is impaired in glycogen-supercompensated muscles of exercised rats (24). With regards to insulin sensitivity, carbohydrate deprivation after exercise results in delayed glycogen restoration and prolonged increase in insulin sensitivity in rat skeletal muscle (2), and, furthermore, insulin-stimulated GLUT-4 translocation-glucose uptake is impaired in supercompensated muscles of exercised rats (23, 24). Thus muscle fuel status may be involved in regulating glucose transport activity and may explain, at least in part, the different magnitudes and durations of increases in glucose transport in exercised skeletal muscles.

Another speculative mechanism by which ES acutely increased GDR may be increased blood flow. DeFronzo et al. (5) have demonstrated that the stimulatory effect of exercise on glucose uptake under physiological hyperinsulinemia is correlated with increased blood flow to exercising muscles, and, in fact, Saltin et al. (44) have found that ES at 50 Hz does increase leg blood flow in a work rate-dependent manner. It is likely that the increase in glucose uptake during and after ES could be due, at least in part, to a better perfusion of the peripheral tissue, which enhances glucose and insulin delivery in stimulated muscles.

All of the subjects who participated in this study were young, healthy individuals; therefore, it has not been elucidated whether similar metabolic effects would be shown in older populations or patients with chronic illnesses, such as Type 2 diabetes. Also, the muscle mass involved in contraction is expected to affect the magnitude of enhancement of both energy and glucose metabolism. A greater increase in glucose uptake might be achieved if more muscles are employed in contraction by using more stimulation electrodes.

In summary, the present study provides fundamental evidence that, similar to voluntary acute exercise, ES to quadriceps muscles results in substantial enhancement of energy consumption and glucose metabolism in humans. Further studies are necessary for testing the safety and efficacy of therapeutic application of ES, which may serve as a valuable adjunct in

the treatment of individuals with glucose intolerance who are limited in their ability to perform physical activities.

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