VIII. 6. Exercise Induced Regulation of Whole-body Glucose Metabolism: A PET Study

Mehedi M.1, 2, Fujimoto T.2, Tashiro M.1, Miyake M.1, Watanuki S.1, and Itoh M.1

1Division of Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University
2Center for the Advancement of Higher Education, Tohoku University

Abstract

Our aim was to visualize homeostatic energy regulation after exercise using 18F-FDG and 3D-PET technique. Five healthy male subjects were studied with 18F-FDG and 3DPET method after exercise task at 40% and 70% VO2max. Additional 6 subjects were studied as controls. ROIs were drawn to assess organ glucose metabolism in the skeletal muscles of thigh, lumbar/gluteal and upperlimb regions and visceral organs such as liver, heart and brain. Relative (standard uptake value, SUV) and absolute glucose metabolic rates (MRGlc) were calculated. Glucose metabolism was increased in the lowerlimb muscles and decreased in the viscera (i.e. Liver and Brain) at mild or moderate exercise loads, suggesting of homeostatic energy redistribution. Good correlation was found between SUV and MRGlc among all organs except for upperlimb muscles. 18F-FDG-3DPET technique of muscles and visceral organs can give objective index of organ energy metabolism in vivo in human, which may have contributions in the sport and rehabilitation science.

Keywords: Exercise, Glucose metabolism, Whole-body, SUV, MRGlc.

Introduction

Regulation of organ metabolic consumption (i.e. glucose and fat) is necessary at exercise task1). During exercise, organ energy metabolism between organs are carried out from whole-body metabolic homeostasis. Previous reports2-3) with semiquantification approach, mentioned the feasibility of glucose metabolic changes in the lower limb skeletal muscles and other organs after fixed exercise load, using 18F-FDG and 3DPET method. Recently, Kemppainen J. and co-workers, assessed the glucose metabolism of single lowerlimb skeletal muscle and myocardium using quantitative analysis4). However, no reports have assessed the
absolute values of glucose metabolism (rMRGlc) at whole-body level after different exercise loads. Nuclear medicine technique, three dimensional positron emission tomography (3DPET) with administration of $^{18}$FDG tracer$^5$, a glucose analogue, is a promising noninvasive imaging tool to elucidate organ activity from glucose metabolism as marker$^6$.

Our purpose was to evaluate workloads inducing whole-body organ glucose metabolism using semiquantitative and quantitative methods. We hypothesize, the redistribution of organ energy metabolism is implemented at whole-body level, when exercise is performed up to moderate workload.

**Methods**

**Subjects**

Eleven healthy male volunteers collaborated with this investigation. All subjects abstained from eating and drinking for at least 5 hours before the experiment. They were asked not to perform any kind of physical exercise from one day before investigation. Five subjects served as exercise group whose ages ranged from 21 to 23 years (Mean 21.80 ± 0.84 y). Another 6 subjects, aged mean 24 ± 5.34 y (Range; 19 ~ 33 y) were studied as resting control maintaining the same study protocol without exercise. $^{18}$FDG dose for controls was in average 42.48 ± 6.63 MBq (Mean±SD.). A written fully informed consent was obtained from each subject before the study. This study protocol was approved by the Clinical Committee for Radioisotope Studies of Tohoku University.

**Study Protocol**

Ergometer bicycle exercise was arranged at 40% and 70% $\dot{V}O_{2\text{max}}$ workloads. $\dot{V}O_{2\text{max}}$ was measured by intermittent exercise on an ergometer bicycle (Monark 818E, Sweden), and the oxygen consumption rate was determined by an automated metabolic unit machine (AE280-S, Minato Co. Ltd. Osaka, Japan). Before the experiment, subjects rested for 20 minutes in a dim lit quiet room. One teflon catheter was inserted to their antecubital veins of the left hand for blood sampling to measure plasma glucose, lactate and insulin. Another teflon catheter was inserted to subject’s antecubital vein of the opposite hand for $[^{18}\text{F}]$FDG administration. Then, they started ergometer bicycle riding at the speed of 60 revolution/min (Monark 818E, Sweden) at 40% and 70% $\dot{V}O_{2\text{max}}$ workloads. $[^{18}\text{F}]$FDG was injected through a catheter at 10 minutes later following exercise task. The radioactivity dose of the exercise group was in average 38.37 ± 2.15 MBq (Mean ± SD). After the injection, subjects continued
to pedal the bicycle for another 30 minutes, completing a total of 40 minutes task. Immediately after intravenous administration of FDG, heated arterialized venous blood was sampled from cubital vein opposite to the injection site. Plasma FDG concentrations were measured both during exercise and PET scan for 24 times. Plasma metabolite concentrations (i.e. Glucose, lactate and insulin) were measured at two points such as pre and post-exercise conditions.

Subjects lay down in supine position on PET table with eyes open following exercise task. The PET room was kept dimmed and quiet. The scan protocol was as follows: a 3 dimensional (3D) whole-body emission scan (3 min × 9 positions) was performed from the knee joint to the vertex followed by transmission scan (3 min × 9 frame) using a PET apparatus (SET2400 W, Shimadzu, Kyoto, Japan). The transmission scan (post-injection mode) was performed with a $^{68}$Ge/$^{68}$Ga external rotating line source (370 MBq at purchase).

**Calculation of glucose metabolism**

ROIs were set on the skeletal muscles of thigh, lumbar/gluteal regions, upper-limb and visceral organs such as liver, heart, brain etc (Fig.1.). To evaluate the rate of glucose utilization, an autoradiographic method was applied using the equation shown below$^{71}$:

$$rMRGlc = \frac{Cp}{LC} \left[ \frac{K_1 k_2^* k_3^*}{k_2^* + k_3^*} \right] \left[ \frac{C^* i(T) - C^* e(T)}{C^* m(T)} \right]$$

In another, semiquantitative analysis (Standard uptake value, SUV) was done by using the following equation:

$$Mean\ ROIcts \ (cps/\ pxls) \times Body\ weight\ (g) \over Injected\ dose\ (\mu Ci) \times Calibration\ factor\ (cps/\ \mu Ci)$$

**Statistical method**

Group comparisons were done by using one-way analysis of variance (ANOVA) and Tukey’s test (post-hoc analysis). The significant differences were set at $p<0.05$. Correlation was calculated using Pearson’s correlation coefficient analysis.

**Results**

FDG uptake was only remarkable in the brain, heart and urinary bladder in the resting subject, while high uptake was visualized in the muscles of exercise conditions (Fig. 1). Glucose metabolism (SUV and MRGlc) was increased in the skeletal muscles of thigh and
lumbar/gluteal regions (p<0.05), and it was decreased in the brain (p<0.05) induced by 40% and 70% \( \dot{V}O_{2\text{max}} \) workloads (Fig. 2). A correlation between SUV and MRGlc was found among organs (i.e. Thigh, lumbar/gluteal muscles, liver, heart and brain), except in the upperlimb muscles (Fig. 3 and Fig. 4). The changes in plasma metabolites were as follows: stable plasma glucose concentrations, an increase (p<0.05) plasma lactate concentration at post-exercise condition of 70% \( \dot{V}O_{2\text{max}} \) (5.3±2.4 mmol/liter) to compare with pre-exercise condition (0.9±0.2 mmol/liter). The plasma insulin concentration was decreased (p<0.05) only at post-exercise workload of 70% \( \dot{V}O_{2\text{max}} \) (2.0±0.7 U/mol) than pre-exercise condition (4.6±1.5 U/mol).

**Discussions and Conclusion**

Organ glucose uptake either increased or decreased almost linearly with the exercise loads up to moderate workload (70% \( \dot{V}O_{2\text{max}} \)). In spite of complexity of energy metabolic controls such as glucose-fatty acid metabolic interaction, aerobic-anaerobic interaction, and involvement of glycogenolysis\(^5\), exercise workloads induced organ glucose metabolism were successfully assessed with \(^{18}\text{FDG}-3\text{DPET} \) technique and two analytical approaches. Organ glucose uptake either increased or decreased almost linearly with the exercise loads up to moderate workload (70% \( \dot{V}O_{2\text{max}} \)), suggesting of homeostatic metabolic control. Semiquantitative method without blood samplings was found useful to estimate a rough trend of glucose consumptions. However, one organ failed to have good correlations between SUV and MRGlc, the upperlimb muscles for example, which demonstrates that semiquantitative approach needs a great care when metabolic rate of glucose utilization changes at whole-body level. \(^{18}\text{FDG}-3\text{DPET} \) technique of muscles and visceral organs can give an objective index of organ energy metabolism *in vivo* in human, which may have contributions in the sport medicine and rehabilitation science.

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References


Figure 1. ROIs procedure in the individual organs, and $^{18}$FDG uptake distributions are visualized at rest and different exercise loads (40% and 70% $\dot{V}O_{2max}$).
Figure 2. Glucose uptake changes ($^{18}$FDG uptake) after exercise loads (40% and 70% VO$_{2\text{max}}$) were visualized in the skeletal muscles (i.e. Thigh, lumbar/gluteal region, and upperlimb) and visceral organs (i.e. Liver, heart and brain), demonstrating two analytical approaches (e.g., MRGlc and SUV).

Figure 3. Correlation between SUV and MRGlc among visceral organs (i.e. Brain, liver and heart).

Figure 4. Correlation between SUV and MRGlc in the skeletal muscles (i.e. Thigh, lumbar/gluteal and upperlimb).