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Computational Model of Glucose Homeostasis During Exercise

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Abstract—**A mathematical model of whole-body metabolism is developed to predict glucose homeostasis during exercise by using a hormonal controller over cellular metabolic processes. Model simulations were validated with experimental data from exercise studies in humans. The exercise-induced changes in hormonal signals modulated metabolic flux rates of various tissues in a coordinated way to maintain blood glucose constant. This study demonstrates the efficacy of a multi-tissue controller to accomplish blood glucose homeostasis by integrating the outputs of tissues under hormonal control. In conclusion, this model can be used as a valuable complement to experimental studies due to its ability to predict what is difficult to measure directly and to provide dynamic information about the system.**

I. Introduction

The goal of this study is to develop a multi-scale mathematical model that relates cellular metabolism in tissue/organ systems connected via the circulation to whole body responses during exercise. The long term goal of this model is to investigate mechanisms for promoting the adaptation to pathogenic conditions (insulin resistance) and reversing it with exercise and dietary intervention. In the initial phase of this work, however, we focused on the development of a model that includes the necessary tissue/organ subsystems and hormonal controllers to predict glucose homeostasis during a moderate intensity exercise bout in normal humans. Exercise provides a useful tool for investigating glucose homeostasis because glucose utilization and production can be increased 2~3 times without perturbing the arterial glucose concentration. The highly coordinated interaction between muscle and liver works to prevent hypoglycemia during exercise.[1] While a few mathematical models have simulated the effects of increased metabolic rate in skeletal muscle during exercise, these models have dealt with limited metabolic pathways in muscle only[2] and none of them is comprehensive enough to include the effects of other organs and hormonal action on glucose homeostasis at the cellular, tissue/organ, and whole-body level.

In this study, we develop a computational model using the general framework and top-down approach of Cabrera et al.[3] that integrates cellular metabolic and transport processes in major tissue/organ systems. In addition to metabolic regulation by ATP/ADP and NADH/NAD^+ at the cellular level, hormonal signals (insulin, glucagon, and epinephrine) provide interaction and coordination among tissues/organs. With respect to glucose homeostasis during moderate intensity exercise, one hypothesis is that exercise-induced change in epinephrine affects the pancreatic secretion of glucagon and insulin, and consequently, a change in the glucagon-to-insulin ratio (GIR = glucagon/insulin) can modulate the metabolic flux rates of different tissues in a coordinated way for the prevention of hypoglycemia.

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II. Model Development

A. Model Framework

The whole-body model consists of seven metabolically distinct tissue/organ compartments connected through the blood circulation (Figure 1): 1) brain, 2) heart, 3) skeletal muscle, 4) gastrointestinal (GI) tract, 5) liver, 6) adipose tissue, and 7) "other tissues". The skeletal muscle compartment represents the muscles in the lower extremity. GI tract includes the splanchnic region (stomach, spleen, intestines) except for liver, and the visceral adipose tissue representing 10% of body fat mass. The "other tissues" compartment includes kidney, upper extremity muscles, and the rest of tissues. In this initial model, arterial oxygen and carbon dioxide concentrations ($C_{a,O2}$, $C_{a,CO2}$) are assumed to be constant. The pancreas serves as a controller of arterial glucagon and insulin concentrations, which depend on arterial glucose and epinephrine concentrations.

B. Dynamic Mass Balances

The concentration dynamics of substrates in each tissue compartment (except "other tissues") are described by dynamic mass balances. Assuming a perfectly mixed lumped tissue-capillary compartment, we can express the dynamic mass balance for *substrate i* in *tissue x* as: [3]

$$V_{eff,x,i}\frac{dC_{x,i}}{dt} = P_{x,i} - U_{x,i} + Q_x(C_{a,i} - \sigma_{x,i}C_{x,i}) \qquad (1)$$

where $V_{eff,x,i}$ is the effective volume of *substrate i* in *tissue x*, $P_{x,i}$ is the production rate of *substrate i*, $U_{x,i}$ is the utilization rate of *substrate i*, Q_x is the blood flow to *tissue x*, $C_{a,i}$ is the arterial concentration of *substrate i*, $\sigma_{x,i}$ is the partition coefficient of *substrate i*, and $C_{x,i}$ is the concentration of *substrate i* in *tissue x*. We consider 9 substrates to be transported between blood and tissue: glucose, pyruvate, lactate, glycerol, alanine, fatty acids, triglyceride, oxygen, and carbon dioxide. For the substrates that exist only in tissue

cells, right side of Eq. (1) contains just the net metabolic reaction term.

Since each tissue is considered as a lumped tissue-capillary compartment, the actual distribution volume ($V_{eff,x,i}$) of *substrate i* differs from the physical tissue volume (V_x).[3] For *substrate i* which exists both in blood and in tissue, $V_{eff,x,i} = 0.93V_x + \sigma_{x,i}(0.07V_x)$; for *substrate i* which exists only in tissue, $V_{eff,x,i} = 0.8V_x$.

The net rate of reaction is expressed in terms of $\phi_{x,k\to i}$, the reaction flux from *substrate k* to *substrate i*:

$$R_{x,i} = P_{x,i} - U_{x,i} = \sum_{k=1}^{m} \beta_{k\to i}\phi_{x,k\to i} - \sum_{k=1}^{n} \beta_{i\to k}\phi_{x,i\to k} \qquad (3)$$

where $\beta_{k\to i}$ is the corresponding stoichiometric coefficient, *m* is the number of reaction fluxes forming *substrate i*, and *n* is the number of reaction fluxes consuming *substrate i*.

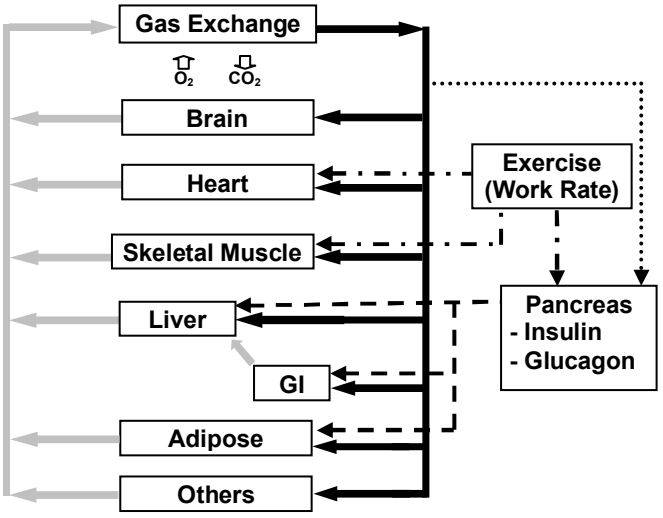

Fig. 1. Whole body system diagram. Each tissue is connected via the blood supply that carries substrates to organs/tissues in arterial blood (black solid arrows). Venous blood (gray solid arrows) leaving these tissues/organs takes away byproducts and becomes arterial blood to re-start the circulation after releasing carbon dioxide and taking up oxygen in lungs (gas exchange). Exercise sends neuroendocrine signals (dash-dot arrows) to heart, skeletal muscle and pancreas. In addition, feedback signal (dotted arrow) from the arterial glucose concentration can be sent to pancreas. Finally, glucagon-insulin ratio signal (dash arrow) from pancreas is sent to liver, GI (gastrointestinal) tract and adipose tissue.

C. Metabolic Reaction Rates

Each substrate is metabolized by various biochemical reactions producing ATP to fuel cellular processes. To define the metabolic reaction fluxes in tissue, it is assumed that each reaction flux is expressed with a general irreversible bi-bi substrate to product enzymatic reaction coupled with controller energy metabolite pairs. The corresponding reaction flux equation in *tissue x* can be expressed as:[4]

$$\phi_{x,X\text{-}Y\to V\text{-}W} = V_{x,X\text{-}Y\to V\text{-}W}\left(\frac{PS^{\pm}}{\mu^{\pm}+PS^{\pm}}\right)\left(\frac{RS^{\pm}}{\nu^{\pm}+RS^{\pm}}\right)\left(\frac{\frac{C_X}{K_X}\cdot\frac{C_Y}{K_Y}}{1+\frac{C_X}{K_X}+\frac{C_Y}{K_Y}+\frac{C_X}{K_X}\cdot\frac{C_Y}{K_Y}}\right) \qquad (4)$$

where $V_{x,X\text{-}Y\to V\text{-}W}$, K_X and K_Y are Michaelis-Menten parameters specific to the reaction process, C_X and C_Y are concentrations of *substrate X* and *Y* in *tissue x*. In this expression, phosphorylation state, $PS^{+} = C_{ATP}/C_{ADP}$, and redox state, $RS^{+} = C_{NADH}/C_{NAD+}$. For some reactions, the effect of these controllers can be in the opposite direction. In this case, $PS^{-}=1/PS^{+}$ and $RS^{-}=1/RS^{+}$. In addition, $\mu^{\pm}$ and $\nu^{\pm}$ are parameters for the metabolic controllers.

D. Hormonal modulation of metabolic reaction fluxes

The interaction via hormonal signals provides a significant feedback mechanism that facilitates glucose homeostasis during exercise. The effect of signaling is characterized by the ratio of glucagon to insulin, which strongly correlates with the change in hepatic glucose production during exercise.[5] Therefore, we assume that the glucagon-insulin ratio affects glycogenolysis and all gluconeogenesis steps in liver as well as lipolysis in adipose and GI tissues. For these reactions, the *metabolic flux f (X-Y→V-W)* in *tissue x* have maximum rate coefficients modulated by the glucagon-insulin ratio:

$$V_{x,f} = V_{x,f}^{0}\cdot\left(1.0+\lambda_{x,f}\frac{(GIR(t)-GIR(0))^{2.0}}{\alpha_{x,f}+(GIR(t)-GIR(0))^{2.0}}\right) \qquad (6)$$

where *GIR* is the ratio of arterial glucagon (C_G) and insulin (C_I) concentrations ($GIR=C_G/C_I$), $V_{x,f}^{0}$ is the resting state maximum rate coefficient, and $\lambda_{x,f}$ and $\alpha_{x,f}$ are parameters for hormonal control effect.

In contrast, heart and skeletal muscles have no receptor for glucagon, but they can respond to an epinephrine signal during exercise. Therefore, we assume that for *metabolic flux f* (viz., glucose phosphorylation by hexokinase, lipolysis, and fatty acid oxidation) in *tissue x* (heart or skeletal muscle), the reaction rate coefficients are modulated as:

$$V_{x,f} = V_{x,f}^{0}\cdot\left(1.0+\lambda_{x,f}\frac{(C_E(t)-C_E(0))^{2.0}}{\alpha_{x,f}+(C_E(t)-C_E(0))^{2.0}}\right) \qquad (7)$$

where C_E is the arterial epinephrine concentration.

E. Glucagon-Insulin Controller

The secretion of glucagon and insulin from the pancreas is affected by blood glucose levels, but during moderate and short duration exercise, a direct neural stimulation and blood epinephrine levels are more significant because the arterial glucose concentration is almost constant. In this work, we postulate that work rate affects circulating epinephrine levels, which then modulates glucagon and insulin secretion by the pancreas. To implement this concept, we adapt an integral

rein controller corresponding to what Saunders et al.[6] developed to maintain the blood glucose level. In our model, an integral rein controller incorporates epinephrine to affect secretion dynamics of insulin assuming an exercise-induced change in the glucagon-insulin ratio.

III. Parameter Estimation

Some parameter values needed to simulate metabolism of a normal human under resting steady-state conditions after an overnight fast (8~12hr) are obtained from the literature, e.g., physiological parameters in tissue/organ compartments of the whole body, arterial blood concentrations for key chemical species involved in transport and metabolism and steady-state uptake/release rates ($Q_x(C_{a,i}-\sigma_{x,i}C_{x,i})$) for specific tissue/organs. Flux balance analysis (FBA) is applied to each tissue compartment to determine intracellular metabolic fluxes at rest. FBA is implemented using steady-state mass balances for all metabolites and flux rates values obtained from the literature. The Michaelis-Menten parameters K_M are set to the initial tissue concentration of the corresponding substrate unless reported in the literature.

Parameters ($\lambda_{x,f}$ and $\alpha_{x,f}$) related to neurohormonal activation during exercise are evaluated by determining values for which simulated model outputs correspond closely with experimental data from human exercise studies. These included whole-body glucose appearance and disappearance rates and arterial substrate concentrations.[7] Thus, parameter values related to these processes are adjusted as needed to make model predictions correspond to quantitative and qualitative physiological responses. However, parameter values related to the glucagon-insulin controller are estimated by optimal least-squares fitting of the model predicted concentrations to the experimental data.[7]

IV. Results

The whole-body model is applied to simulate metabolic responses during moderate intensity exercise, viz., a cycle ergometer test with a work rate of 150 W maintained for 60 min. A step change in a work rate (150W) generated 5-fold increase in epinephrine concentration (data not shown), which via the glucagon-insulin controller, induced a 40% decrease in the arterial insulin concentration and a 15% increase in the arterial glucagon concentration over 60 min of exercise making their ratio increased 90% (Figure 2). The exercise induced hormonal change modulated fluxes in affected tissues, and consequently, the whole-body glucose production increased about 3 fold (from 0.73 to 1.98 mmol/min) at the end of 60 min exercise (Figure 3). The time of profiles of the rate of glucose uptake and utilization by skeletal muscle mimicked that of glucose production by the liver. As a consequence, no significant (<3%) change occurred in arterial glucose concentration throughout exercise due to off-setting changes in whole-body glucose production and utilization rates (Figure 4), which maintain glucose homeostasis during exercise.

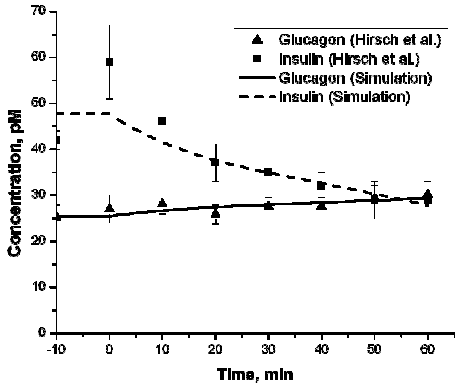

Fig. 2. Dynamic responses of arterial glucagon and insulin concentrations to a step increase in work rate from resting state at 0 min.

The increased glucagon-insulin ratio during exercise changed glucose production in liver. Net hepatic glycogen breakdown increased from 0.38 to 1.48 mmol/min, while net gluconeogenesis rate increased from 0.35 to 0.52 mmol/min (Figure 5). The relative contribution of gluconeogenesis continuously decreased to 26% of total glucose production at 60 min starting from 48% at rest.

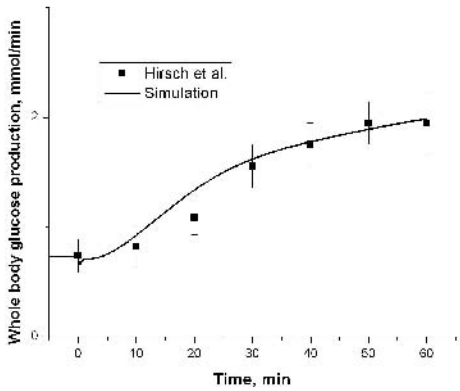

Fig. 3. Whole body glucose production during 60 min exercise.

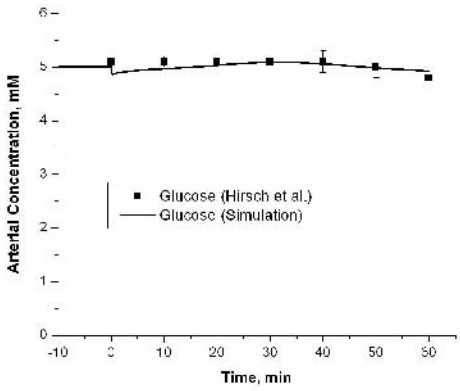

Fig. 4. Dynamic response of arterial glucose concentration to a step increase in work rate from resting state at 0 min.

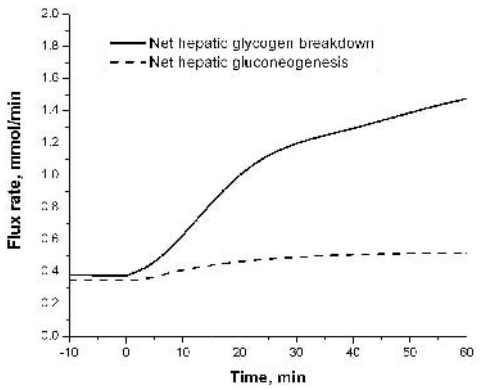

Fig. 5. Dynamic responses of hepatic glycogenolysis and gluconeogenesis to a step increase in work rate from resting state at 0 min.

V. Discussion

In this study, we developed and validated a multi-scale model of fuel homeostasis which 1) differentiates tissues with distinct metabolic pathways, 2) includes transport and biochemical reactions of major fuel sources, 3) incorporates the effect of hormonal control by both insulin and glucagon to regulate the metabolic processes in each tissue, and 4) consequently, relates cellular metabolic processes and their regulation to whole body responses.

To our knowledge, this is the first mechanistic model of glucose homeostasis that links cellular metabolism to whole-body responses and incorporates effects of hormonal control on fuel metabolism of various tissues/organs. Bergman et al.[8] developed "minimal models" to quantify the degree of insulin resistance from a glucose tolerance test. While these models are simple in nature, they show good clinical applicability to be tailored to the individual subject, which is not possible with our current model. However, these models only include the effects of insulin as well as insulin-independent/dependent tissue compartments. Thus these models are not general enough to be applied to other kinds of physiological conditions (e.g., exercise) or pharmacological interventions.

Since blood glucose is regulated by two hormones that act in opposite directions to inhibit the secretion of each other, the balance between them is more important than individual absolute levels.[6] Thus, it is very significant to include both glucagon and insulin to describe glucose homeostasis. Saunders et al.[6] applied the concept of integral rein control with two hormones in mathematical model of glucose regulation. The model, however, was not validated with the experimental data. In contrast, our mathematical model of whole body glucose homeostasis includes all important fuel sources (glucose, glycogen, fatty acids, TG, lactate, etc.) and distinguishes tissue/organs with different metabolic characteristics.

Although our model simulations compare well with most experimental data, one obvious limitation is that the dynamics of arterial lactate concentration do not correspond to experimental data (Figure 6C). A possible source of this discrepancy is the assumption of homogeneity in the tissue-cells compartment of skeletal muscle. Recently, Zhou et al.[4] showed that distinguishing cytosol and mitochondria in this compartment leads to different dynamics of cytosolic and mitochondrial NADH/NAD^+ ratios and to more physiological lactate concentration time profiles. Therefore, future modifications to the model should incorporate distinct blood and extravascular tissue compartments and distinguish cytosol from mitochondria in the tissue-cells compartment.

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