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Insulin sensitivity predictions in individuals with obesity and type II diabetes mellitus using mathematical model of the insulin signal transduction pathway

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ABSTRACT

Mathematical modeling approaches have been commonly used in complex signaling pathway studies such as the insulin signal transduction pathway. Our expanded mathematical model of the insulin signal transduction pathway was previously shown to effectively predict glucose clearance rates using mRNA levels of key components of the pathway in a mouse model. In this study, we re-optimized and applied our expanded model to study insulin sensitivity in other species and tissues (human skeletal muscle) with altered protein activities of insulin signal transduction pathway components. The model has now been optimized to predict the effect of short term exercise on insulin sensitivity for human test subjects with obesity or type II diabetes mellitus. A comparison between our extended model and the original model showed that our model better simulates the GLUT4 translocation events of the insulin signal transduction pathway and glucose uptake as a clinically relevant model output. Results from our extended model correlate with O'Gorman's published *in-vivo* results. This study demonstrates the ability to adapt this model to study insulin sensitivity to many biological systems (human skeletal muscle and mouse liver) with minimal changes in the model parameters.

1. Background

The use of mathematical modeling provides strong predictions of physiological behavior in signaling systems. The insulin signal transduction pathway, a complicated signaling network comprised of cross-interacting components and feedback loops, has been extensively studied using computational analysis such as mathematical modeling. These studies emphasized different aspects of the insulin signal transduction pathway, including insulin binding to its receptor, GLUT4 translocation, and glucose homeostasis [1,2]. We previously introduced a revised and expanded mathematical model of the pathway that is capable of predicting insulin sensitivity in biological systems, and tested this model using gene expression data from livers of a mouse model of glycerol kinase deficiency of key components of the pathway as the model input [3]. The last study demonstrated that our extended model was able to simulate the glucose uptake levels of glycerol kinase knockout mice using published gene expression profiles of microarray analysis.

Our model is an extension of an established insulin signaling model developed by Sedaghat et al. [1]. Sedaghat's model provided the basis of simulating several of the most accepted mechanisms of the insulin signal transduction pathway, including the activation of phosphoinositide 3-kinase (PI3K) and the translocation of glucose transporter (GLUT4) to the plasma membrane. In the previous study, we modified Sedaghat's model to overcome its shortcomings, including the incorporation of components of the pathway that have been elucidated since Sedaghat's paper was published into the model as well as the ability to predict new sets of parameter values based on different biological systems and tissue types using *in-vivo* published results [3]. In this manuscript, we extend our model to other species and tissues (human skeletal muscle) including re-optimization for these tissues.

1.1. Exercise in obesity/type II diabetes

Exercise has been shown to prevent or improve obesity and insulin sensitivity in individuals with T2DM [4,5], however the molecular mechanism of this is still unclear. Several studies have shown an association between short-term exercise and alterations in gene expression, protein or protein phosphorylation levels of key components in the insulin signal transduction pathway [4,6,7]. Short-term exercise increases

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the concentration of active insulin receptor as well as insulin receptor substrate-1 (IRS1) phosphorylation in both obese and T2DM patients [6]. Exercise training has also been shown to increase overall insulin signaling transduction and glucose uptake rates in skeletal muscles of rodents [7]. In one particular study, O'Gorman et al. assessed the effects of short-term exercise on insulin signal transduction, specifically measuring whole-body insulin-mediated glucose clearance of obese non-diabetic and obese T2DM subjects [4]. They found differences in the protein activity levels of IRS1, phosphorylated Akt, and AS160 between the study groups. They showed that T2DM subjects have increased GLUT4 protein content due to exercising. Collectively, this data showed that short-term exercise improves fasting glucose and insulin-mediated glucose disposal in obese type II diabetic subjects but not in obese non-diabetic human subjects.

It is not a novel idea to utilize mathematical modeling approaches to study the association of insulin sensitivity and exercise. Derouich et al. took a minimal yet comprehensive approach to simulate the effect of physical exercise on insulin-dependent diabetic individuals [8,9]. They incorporated simple linear relationships between insulin secretion and glucose disappearance [10], as well as blood glucose control dynamics from insulin-dependent diabetes therapy [11]. Since the development of that model, researchers have made significant progress toward elucidating components in the insulin signal transduction pathway. Therefore, we can take advantage of the new findings and perform better simulations in studying the relationship of exercise and insulin signal transduction. In this study, we propose a significantly different approach from other modeling studies to further examine the effect of exercise on insulin sensitivity in humans using expression levels of key components of insulin sensitivity.

The data reported in O'Gorman et al. includes gene expression levels and protein activity levels of key players (*i.e.* IRS1, Akt, AS160) in the insulin signal transduction pathway between obese non-diabetic and obese T2DM human subjects [4]. Therefore, it allows for applications of O'Gorman's data into our expanded mathematical model to simulate the GLUT4 translocation and glucose uptake rate in response to exercise training. The dataset would be inapplicable to other existing mathematical models because those models did not account for intermediate components, such as AS160, that have critical roles in GLUT4 translocation.

Our expanded model is used to simulate GLUT4 translocation to the plasma membrane and subsequently predict glucose clearance, in response to a given dose of insulin. The extent of the glucose uptake is a measure of insulin sensitivity. In this study, we updated our previous model's parameter values to effectively simulate insulin signaling in human skeletal muscle. We assessed our new model by inputting the dataset from O'Gorman et al., which showed differential gene expression/protein activity levels in humans. We then compared our simulated results of glucose uptakes to the results in the published *in vivo* studies [4,5].

2. Results

To re-optimize our model, we determined new rate constants suitable for insulin sensitivity prediction in human skeletal muscle, and gathered experimental data from the published literature of the chemical kinetics of the key components in the insulin signal transduction in humans. Data presented in Frosig et al. was used to determine rate constants k14a, which represents the kinetics of the AS160 phosphorylation reaction [12,13]. Frosig et al. conducted exercise training sessions on healthy individuals and measured protein activity of key components of the insulin signal transduction pathway, including Akt1, AS160, and GLUT4 (Fig. 4.5, Frosig et al. [13]). Glucose uptake levels were also obtained from the study subjects as a result of the exercise training sessions (Fig. 3A, Frosig et al. [13]). We determined the optimal rate constants that would simulate glucose uptake response best fitted to the published glucose uptake data of Frosig et al. [13]. By using the chosen rate constant values, we simulated the AS160-glucose uptake fold change relationship observed in the scatterplot (Fig. 1). Time response curves were simulated for both untrained and trained groups with an insulin dose of 5 μM for 120 min. Parameter values were optimized so that the simulated response curves matched well with the experimental response from this particular human study.

2.1. Expanded model predicts exercise stimulated improvement in insulin sensitivity in agreement with previous experimental data

We validated our expanded model to see if it would mimic published experimental data from O'Gorman et al. [4] (dataset in Table 1). The dataset includes differential expression in IRS 1-associated PI3K, AS160 phosphorylation, and total GLUT4 protein between human subjects with T2DM and human subjects with obesity. They also provided two-hour oral glucose tolerance test results and glucose infusion rates of each group, which allowed for the comparison of the simulated glucose uptake rate from our model to experimental references. In our simulations, we modeled insulin sensitivity by predicting the glucose uptake rate with an insulin dose of 50 nM for 120 min, conditions that were similar to what was done to the subjects in the glucose tolerance test. The simulated maximum GLUT4 translocation was greater (30.5%) for obese subjects who performed seven days of exercise compared to the obese subjects who did not exercise (Fig. 2A). For subjects with T2DM, glucose clearance was greater (55.6%, $p < 0.05$) for those who performed training for seven days compared to those who did not exercise (Fig. 2B). The total amount of glucose cleared by the system was significantly higher for subjects with T2DM who trained for seven days, but not significantly higher for the obese subjects who exercised. Using the simulated glucose uptake and GLUT4 translocation results, we examined whether our expanded model could simulate experimental data in O'Gorman et al. more effectively than Sedaghat's model. Therefore, we applied O'Gorman's dataset to the original setup in Sedaghat's model, then compared the simulated glucose uptake rate between our expanded model and Sedaghat's model (Fig. 3). Both models agree with the findings reported by O'Gorman et al., suggesting that exercising improves insulin sensitivity for both obese individuals and individuals with T2DM. However, our expanded model shows better correlation with the experimental data than Sedaghat's model, although the difference in fold changes between the models is not statistically

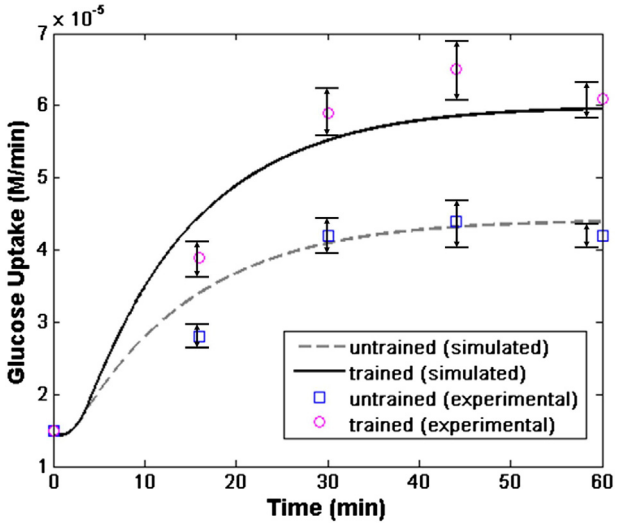

Fig. 1. Comparison of simulated glucose uptake and experimental glucose uptake as a result of exercise training. Experimental results were based on data from the Frøsig et al. study [13]. Data points were presented as open circles (trained) and open squares (untrained) in the figure. Simulated response curves were presented as solid and dotted lines. Error bars shown are accounting for the standard error of the data reported in Frøsig's study (Fig. 3A of Frøsig et al.).

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