Insulin Sensitivity and the Insulin-Responsive Glucose Transport System

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Submitted to the faculty of the graduate school
in partial fulfillment of the requirements
for the degree
Doctor of Philosophy
in the Department of Physiology and Biophysics
Indiana University
July 1997

Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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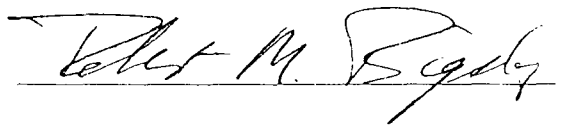

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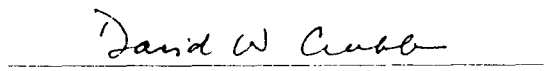

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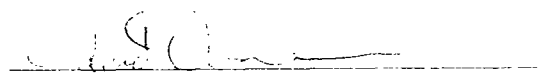
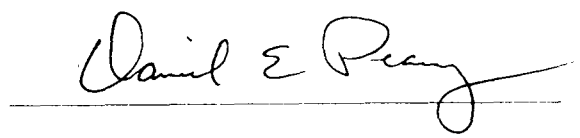


David Donner, Ph.D.

May 9, 1997



Daniel E. Peavy, Ph.D.

Abstract

Shichun Bao

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Insulin resistance pertaining to regulation of glucose metabolism is important in the pathogenesis of diabetes mellitus, obesity, and cardiovascular disease risk. Insulin stimulates glucose transport via translocation of the GLUT 4 glucose transporter isoform from intracellular pools to the plasma membrane. Defects causing insulin resistance have not been fully elucidated, but are associated with depleted numbers of cellular GLUT 4 in fat and impaired GLUT 4 translocation in muscle due to abnormal trafficking of GLUT 4-containing vesicles. This work illustrates that the glucose transport system is a primary determinant of insulin sensitivity and substrate metabolism, and explores mechanistic aspects of glucose transport function. The major findings and conclusions are as follows:

1) In primary cultured rat adipocytes, induction of insulin resistance by prolonged exposure to high insulin and glucose involved decreased glucose transport activity, whereas other metabolic pathways of insulin action were not affected (protein synthesis, glucose oxidation and incorporation into lipids) or enhanced (glycogen synthesis). This differential regulation of insulin's bioeffects indicates that insulin resistance is likely due to effects on the glucose transport effector system and not on common signal transduction pathways.

2) Transgenic mice overexpressing GLUT 4 display hypersensitivity to insulin, and metabolize more carbohydrate and less lipid during exercise despite hypoglycemia and increased availability of free fatty acids. Increased carbohydrate metabolism inhibits lipid oxidation such that there is no change in overall energy expenditure. This observation indicates that the glucose-fatty acid cycle (or Randle hypothesis) may in fact work in reverse. Enhanced carbohydrate utilization in transgenic mice is facilitated by accelerated glycogenolysis. Glycogen content has an overriding regulatory influence on I-form glycogen synthase activity. Thus, a primary perturbation in the glucose transport system has important effects on fuel metabolism and insulin sensitivity.

3) The major pool of insulin-responsive GLUT 4 derives from vesicles adjacent to the endofacial surface of the plasma membrane (PM) and PM-invaginations in rat adipocytes. It is not sensitive to brefelin A, and does not involve the Golgi apparatus. Cellular trafficking of GLUT 4 is complex and involves multiple subcellular compartments.

4) More than ten Rab isoforms of small G-proteins are expressed in human skeletal muscle. The plethora of Rab GTP-ases are indicative of a high degree of regulated vesicular traffic. However, the potential role of specific Rab isoforms in GLUT 4 translocation and insulin resistance does not rely on a change in steady state mRNA levels.

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