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Review

Lipid oversupply, selective insulin resistance, and lipotoxicity: Molecular mechanisms

Jose Antonio Chavez [a], Scott A. Summers [a,b,*]

[a] Stedman Center for Nutrition and Metabolism Research, Duke University Medical Center, Durham, NC 27704, USA
[b] Program in Cardiovascular and Metabolic Disorders, Duke-NUS Graduate Medical School, Singapore, 228414 Singapore

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ABSTRACT

The accumulation of fat in tissues not suited for lipid storage has deleterious consequences on organ function, leading to cellular damage that underlies diabetes, heart disease, and hypertension. To combat these lipotoxic events, several therapeutics improve insulin sensitivity and/or ameliorate features of metabolic disease by limiting the inappropriate deposition of fat in peripheral tissues (i.e. thiazolidinediones, metformin, and statins). Recent advances in genomics and lipidomics have accelerated progress towards understanding the pathogenic events associated with the excessive production, underutilization, or inefficient storage of fat. Herein we review studies applying pharmacological or genetic strategies to manipulate the expression or activity of enzymes controlling lipid deposition, in order to gain a clearer understanding of the molecular mechanisms by which fatty acids contribute to metabolic disease.

1. Introduction

> "Gluttony is the source of all our infirmities, and the fountain of all our diseases. As a lamp is choked by a superabundance of oil, a fire extinguished by excess of fuel, so is the natural health of the body destroyed by intemperate diet." Robert Burton, English writer, philosopher and humorist, 1621

In a 1992 paper entitled "What if Minkowski had been ageusic—an alternative angle on diabetes," Dennis McGarry suggested that the glucose-centric view of diabetes had led researchers astray, and that the disease would be "more readily understood if viewed in the context of underlying abnormalities of lipid metabolism" [1]. This seminal paper challenged existing dogma about the aetiology of the disease, and introduced a new and controversial model suggesting that increased action of insulin, specifically its ability to drive lipid synthesis in the liver, rather than insulin resistance, was the key feature in the progression towards diabetes. Some 17 years later, we know that Dr. McGarry was not only correct in many of his predictions, but that disorders in lipid metabolism and the excess delivery of fat to peripheral tissues underlie most of the more prevalent diseases affecting mankind. In the article below, we discuss progress elucidating the molecular mechanisms by which abnormalities in lipid metabolism contribute to diabetes and other metabolic diseases.

The psychological and economic toll of diabetes is well documented, and the increasing rate of occurrence of the condition is disconcerting and unequivocal [2]. The astounding proliferation of the disease is undoubtedly related to population changes in body composition, as the prevalence of obesity in the USA has risen from percentages in the mid-teens at the time of Dr. McGarry's article to nearly 33% today [3]. With obesity rates increasing in developed and developing countries across the globe [4], the World Health Organization estimates that a staggering number of individuals are currently dealing with complications of disrupted lipid homeostasis, 1.6 billion adults are overweight, 400 million are obese, and 180 million are diabetic [5]. Cardiovascular disease, which is the major complication of diabetes, is the cause of death of 17 million [6].

Based on our review of the literature, we surmise that the metabolic diseases associated with obesity, including diabetes and cardiovascular disease, derive from a common molecular pathogenesis characterized of two independent stages: (a) *selective* insulin resistance; and (b) lipotoxicity (Fig. 1).

- *Stage One: Selective Insulin Resistance.* When circulating glucose reaches a critical threshold level, pancreatic β-cells secrete insulin,

* Corresponding author. Program in Cardiovascular and Metabolic Disorders, Duke-NUS Graduate Medical School, 8 College Road, Singapore 228414, Singapore. Tel.: +65 6516 8793; fax: +65 6221 6757.
E-mail address: scott.summers@duke-nus.edu.sg (S.A. Summers).

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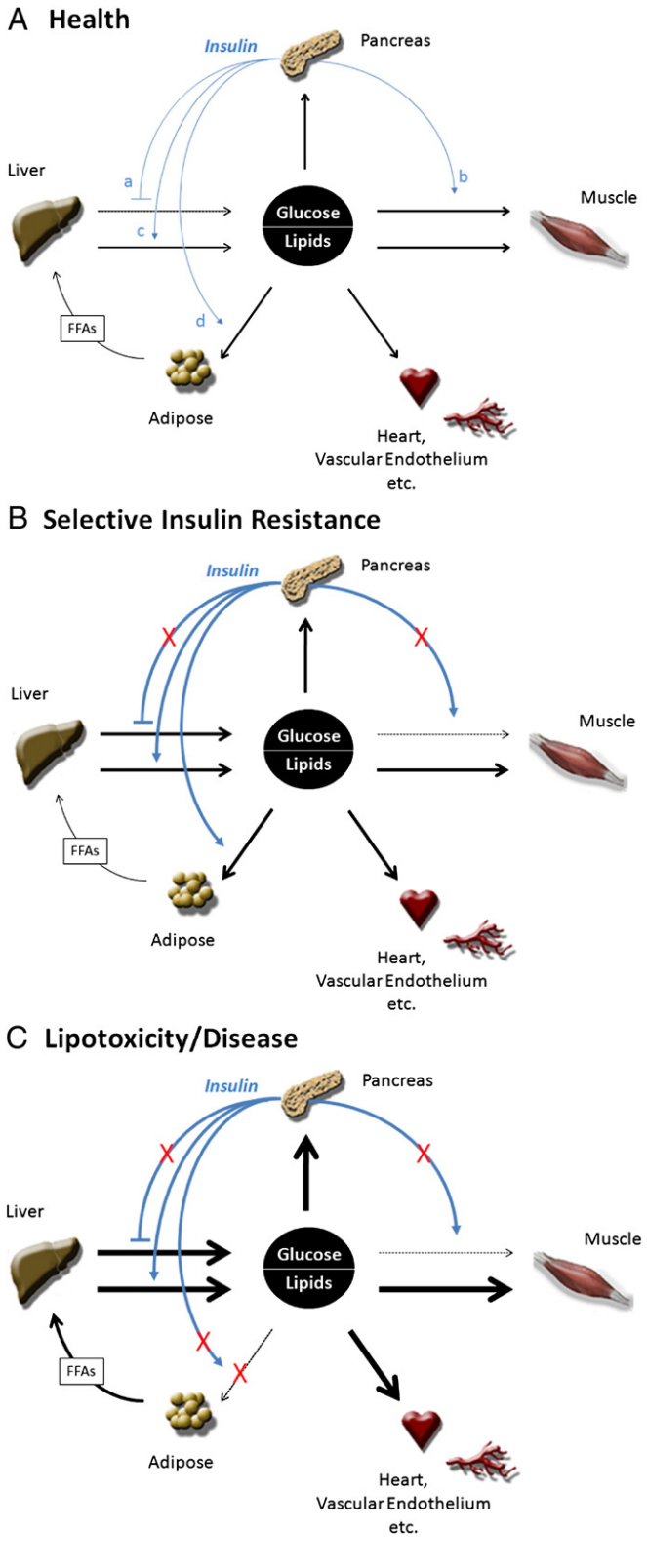
the major anabolic hormone in the body. Insulin has two major actions: to lower circulating glucose levels by facilitating its uptake into skeletal muscle while inhibiting its production by the liver; and, to promote the storage of available nutrients, predominantly in the form of glycogen and fat. Obese individuals display a decreased capacity for insulin-stimulated glucose disposal, as muscle fibres adjust to utilize the calorically dense fatty acids, rather than glucose, as a primary energy source. However, insulin-stimulated lipogenesis, particularly in the liver and adipose tissue, is unaltered or enhanced. This selective insulin resistance is one of several factors which predispose individuals to cardiovascular disease and diabetes [7].

The relative importance of insulin resistance in the pathogenesis of metabolic disease is subject to debate. At best, insulin resistance is a benign predictor of metabolic disease—an independent marker of a condition where the supply of nutrients exceeds demand, and muscle is adapting to oxidize lipids, while sparing glucose. At worst, this selective insulin resistance exacerbates and accelerates the path towards metabolic disease, as it promotes hyperinsulinemia, leading to an increase in triglyceride synthesis and enhanced delivery of lipoprotein-bound fats to peripheral tissues.

- *Stage Two: Lipotoxicity in Peripheral Tissues.* Diseases related to obesity probably result from the delivery of lipids to peripheral tissues in excess of their oxidative or storage capacities. Indeed, experimental manipulations aimed to enhance lipid delivery to peripheral tissues (e.g. pancreatic β-cells or the heart) or prevent their storage in white adipose tissue is sufficient to recapitulate many of the features of these diseases [8-19]. Moreover, pharmacological therapies for warding off the condition almost invariably reduce the accumulation of ectopic fat in non-adipose tissues (e.g. thiazolidienediones, metformin, or statins).



Ultimately, both of these stages likely result from the excess delivery of fat to peripheral tissues, and the body appears capable of sensing small changes in cellular lipids. During selective insulin resistance, elevation in intracellular lipid metabolites leads to an inhibition of GLUT4 glucose transporters, thus decreasing net rates of glucose influx into the cell. During lipotoxicity, this increased lipid deposition leads to cellular events that compromise tissue function, such as ER and oxidative stress, apoptosis, etc. However, an understanding of the mechanisms underlying these varied responses has been elusive.

In virtually all tissues, fatty acids face one of three major metabolic fates: (a) they can be converted to glycerolipids, including triglycerides, diglycerides, and major membrane phospholipids (Fig. 2); (b) they can be converted to sphingolipids, including sphingomyelin and ceramide (Fig. 3); and, (c) they can be oxidized for energy (Fig. 4). As the genes and enzymes that control these anabolic and catabolic pathways have been sequenced and characterized, accompanying experiments manipulating their expression and/or activity has revealed that modulating rates of lipid synthesis and degradation has profound effects on insulin-sensitivity, diabetes, and cardiovascular disease.

2. Manipulation of glycerolipid synthesis: impact on selective insulin resistance and lipotoxicity

Energy-dense triglycerides (TAGs) have two major physiological roles: first, they are energy stores, and their accumulation, preferentially in adipocytes, allows organisms to prepare for periods when

Fig. 1. Schematic diagram depicting the flux of nutrients during the proposed stages of metabolic disease. (A) In healthy individuals, insulin facilitates postprandial nutrient deposition by (a) inhibiting hepatic glucose production, (b) stimulating glucose uptake into muscle, and promoting triglyceride synthesis in (c) liver and (d) adipose. (B) The obese become selectively resistant to insulin effects on glucose metabolism, such that muscle glucose transport is blocked and hepatic glucose output is enhanced (denoted by red X's). However, other effects of insulin remain intact, and the enhanced lipogenesis in the liver leads to increased circulating triglyceride levels (i.e. VLDLs). As circulating insulin levels rise, due to the residual glucose in the blood, the lipogenic effects of the hormone become dominant, and a vicious cycle ensues. Increased production of triglycerides leads to an increasing rate of their delivery to peripheral tissues, greater insulin resistance, more profound hyperinsulinemia, and exacerbation of the lipid synthesis effects of the hormone. (C) The final stages of metabolic disease involve additional defects in the adipocyte. Impairments in adipocyte plasticity or storage capacity limit its utility as a reservoir for excess fat. Moreover, impairment of insulin action in the tissue leads to enhanced lipolysis, further increasing delivery of fatty acids to the liver. Ultimately, lipid delivery to peripheral tissues exceeds their storage and oxidative capacity, and tissue damage ensues.