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Review

Glycerolipid/free fatty acid cycle and islet β-cell function in health, obesity and diabetes

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ABSTRACT

Pancreatic β-cells secrete insulin in response to fluctuations in blood fuel concentrations, in particular glucose and fatty acids. However, chronic fuel surfeit can overwhelm the metabolic, signaling and secretory capacity of the β-cell leading to its dysfunction and death – often referred to as glucolipotoxicity. In β-cells and many other cells, glucose and lipid metabolic pathways converge into a glycerolipid/free fatty acid (GL/FFA) cycle, which is driven by the substrates, glycerol-3-phosphate and fatty acyl-CoA, derived from glucose and fatty acids, respectively. Although the overall operation of GL/FFA cycle, consisting of lipolysis and lipogenesis, is "futile" in terms of energy expenditure, this metabolic cycle likely plays an indispensable role for various β-cell functions, in particular insulin secretion and excess fuel detoxification.

In this review, we discuss the significance of GL/FFA cycle in the β-cell, its regulation and role in generating essential metabolic signals that participate in the lipid amplification arm of glucose stimulated insulin secretion and in β-cell growth. We propose the novel concept that the lipolytic segment of GL/FFA cycle is instrumental in producing signals for insulin secretion, whereas, the lipogenic segment generates signals relevant for β-cell survival/death and growth/proliferation.

Contents

Abbreviations: ABHD6, α/β-domain containing hydrolase-6; ADRP, adipocyte differentiation-related protein; AGPAT, 1-acyl-*sn*-glycerol-3-phosphate acyltransferase; AMPK, AMP activated protein kinase; ATGL, adipose triglyceride lipase; CGI-58, comparative gene identification 58 protein; CPT-I, carnitine palmitoyltransferase I; DAG, diacylglycerol; DAGL, DAG lipase; DGAT, DAG acyltransferase; ER, endoplasmic reticulum; FFA, free fatty acid; GL, glycerolipid; GPAT, glycerophosphate acyltransferase; Gro3P, glycerol-3-phosphate; GSIS, glucose-stimulated insulin secretion; HSL, hormone sensitive lipase; LPA, lysophosphatidic acid; MAG, monoacylglycerol; MAGL, MAG lipase; PA, phosphatidic acid; PKC, protein kinase C; PPAR, peroxisomal proliferator activated receptor; T2D, type-2 diabetes; TG, triglyceride; ZDF, Zucker diabetic fatty; ZF, Zucker fatty; ZF-Px, 60% pancreatectomized ZF rat.

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1. Introduction

In mammalian cells lipid and glucose metabolism are interlinked by a central pathway, called the glycerolipid/free fatty acid (GL/FFA) cycle, also known as triglyceride/fatty acid cycling. The GL/FFA cycle is initiated by combining the glucose-derived glycerol-3-phosphate (Gro3P) with the fatty acid-derived fatty-acyl-CoA. GL/FFA cycling is a process of fatty acid esterification with glycerol to form triacylglycerol (TG), followed by the hydrolysis of TG to re-generate glycerol and fatty acids, which can re-enter the cycle (Fig. 1). Thus, it is known that in various tissues most of the FFA released in the cytoplasm upon lipolysis is immediately re-esterified, even at steady state levels of TG and FFA (Newsholme and Crabtree, 1976). This process is indeed *futile* as 7 ATP molecules are consumed per each complete turn of the cycle (Fig. 1), thus releasing heat. However, looking at this cycle with a novel angle and beyond its roles in fuel storage/mobilization and thermogenesis, a novel picture emerges related to fuel signaling. Indeed, this constitutively active metabolic pathway appears to be a *vital* cellular process that plays an important role in various functions. These include the stimulation of cells by glucose and FFA to promote their growth and modulate gene expression, detoxification of excess fuels, the activation of fuel sensing effectors such as AMP-activated protein kinase (AMPK) and SIRT-1, and the regulation of insulin secretion that this review will examine in detail.

2. GL/FFA cycling processes in individual cells, in organs and among tissues

The importance of the GL/FFA cycle for whole body homeostasis (Fig. 1) becomes evident considering that this pathway's esterification (lipogenesis) and hydrolytic (lipolysis) arms generate glycerol, FFA and many lipid signaling molecules, and that abnormalities associated with this cycle lead to pathological conditions such as insulin resistance, type-2 diabetes (T2D) (Prentki and Madiraju, 2008), non-alcoholic fatty liver disease (Larter et al., 2010), and even cancer (Nomura et al., 2010).

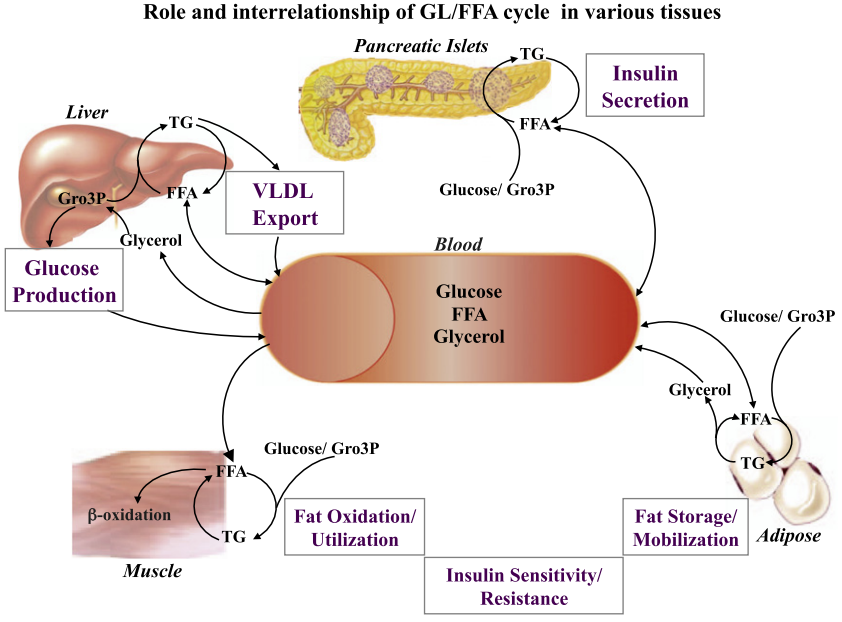

Fig. 1. Role and interrelationship of GL/FFA cycle in various tissues. Various tissues in the body share the metabolites and substrates of GL/FFA cycling through the blood, and this enables the GL/FFA cycling processes in the body tissues to be inter-linked and thus exert its signaling/metabolic regulation in a collective manner in the whole body. Thus, a high rate of GL/FFA cycling in adipose tissue supplies a major portion of glycerol and FFA to the other tissues through blood. Glycerol is used mostly by the liver for gluconeogenesis to produce glucose. FFA can be used by heart and skeletal muscle for both GL/FFA cycle and for β-oxidation, whereas in liver, it is used for TG synthesis and VLDL assembly and secretion. Excessive release of FFA from adipose can lead to insulin resistance while removal of FFA in skeletal muscle enhances insulin sensitivity. Besides adipose, other tissues that lack glycerol kinase also release glycerol through GL/FFA cycling into blood. Liver and skeletal muscle can produce and also utilize glycerol as they have glycerol kinase. Most of the FFA produced in the tissues through the lipolytic segment of the cycling are fed back into lipogenesis or released into blood. VLDL secreted from the liver into blood can contribute to FFA through lipoprotein lipase activity (not depicted). TG formed in adipose tissue is stored as lipid droplets. Ample evidence indicates that GL/FFA cycling is essential for glucose induced insulin secretion in pancreatic β-cells, probably by the generation of critical signaling molecules.