Molecular Aspects of Medicine 46 (2015) 21–33

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

# Molecular pathophysiology of hepatic glucose production

Kfir Sharabi, Clint D.J. Tavares, Amy K. Rines, Pere Puigserver *

*Department of Cancer Biology, Department of Cell Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA*

ARTICLE INFO

*Article history:*
Received 9 September 2015
Accepted 9 September 2015
Available online 5 November 2015

*Keywords:*
liver
glucose
gluconeogenesis
insulin
glucagon

ABSTRACT

Maintaining blood glucose concentration within a relatively narrow range through periods of fasting or excess nutrient availability is essential to the survival of the organism. This is achieved through an intricate balance between glucose uptake and endogenous glucose production to maintain constant glucose concentrations. The liver plays a major role in maintaining normal whole body glucose levels by regulating the processes of de novo glucose production (gluconeogenesis) and glycogen breakdown (glycogenolysis), thus controlling the levels of hepatic glucose release. Aberrant regulation of hepatic glucose production (HGP) can result in deleterious clinical outcomes, and excessive HGP is a major contributor to the hyperglycemia observed in Type 2 diabetes mellitus (T2DM). Indeed, adjusting glycemia as close as possible to a non-diabetic range is the foremost objective in the medical treatment of patients with T2DM and is currently achieved in the clinic primarily through suppression of HGP. Here, we review the molecular mechanisms controlling HGP in response to nutritional and hormonal signals and discuss how these signals are altered in T2DM.



**Contents**



* Corresponding author. Dana-Farber Cancer Institute, 450 Brookline Av. CLSB-11144, Boston, MA 02215, USA. Tel.: +1 617 582 7977; fax: +1 617 632 5363.
*E-mail address:* pere_puigserver@dfci.harvard.edu (P. Puigserver).

http://dx.doi.org/10.1016/j.mam.2015.09.003
0098-2997/

## 1. Introduction

Abnormal concentrations of glucose in plasma result in deleterious effects at the whole organism level. Glucose is the main energy source for the brain and decreased plasma glucose levels (hypoglycemia) can lead to impaired brain function and death. Conversely, increased plasma glucose levels (hyperglycemia), a major clinical symptom of diabetes, dramatically increase the risk of various macrovascular and microvascular complications.

Glucose homeostasis is balanced by nutrient sensing and hormonal signaling intracellular mechanisms that control tissue-specific rates of glucose utilization and production. Among the tissues contributing to the maintenance of normal ranges of blood glucose levels are the liver, skeletal and cardiac muscle, fat and brain. After a carbohydrate meal, ~33% of the glucose is taken up by the liver, another ~33% is taken up by muscle and adipose tissues, and the remaining glucose is taken up by the brain, kidney and red blood cells (RBC) (Moore et al., 2012). Insulin and glucagon are two central glucose-dependent counterregulatory hormones that orchestrate the peripheral tissues' responses to control rates of utilization and production of glucose to maintain glycemia within narrow ranges. Indeed, the resistance of these tissues to insulin is the major contributor to impaired glucose homeostasis leading to hyperglycemia and to the development of type 2 diabetes mellitus (T2DM) (Samuel and Shulman, 2012).

The liver plays a major role in maintaining glucose homeostasis, as it is the main organ for glucose storage, in the form of glycogen, as well as endogenous glucose production. When nutrients are available, insulin is secreted from pancreatic β cells and promotes hepatic glycogen synthesis and lipogenesis. When nutrients become scarce, insulin levels are decreased and glucagon is secreted from pancreatic α cells to promote hepatic glucose production (HGP) to meet brain and RBC energetic demands. HGP is achieved by glycogen breakdown (glycogenolysis) as well as by de novo glucose synthesis from available precursors (gluconeogenesis). Increased rates of HGP, as observed in patients with T2DM, significantly impair glucose homeostasis and significantly contribute to hyperglycemia (Lin and Accili, 2011). Therefore, controlling the rates of HGP is one of the major targets for the treatment of T2DM patients. In this review, we will focus on the molecular mechanisms underlying the nutrient and hormonal regulatory control of HGP.

## 2. Whole body glucose homeostasis

Blood glucose concentrations in normal healthy individuals are normally maintained at ~90 mg/dl. This is a result of an intricate balance between endogenous glucose production and glucose removal from the blood stream, which are dynamically regulated by hormonal and nutritional signals. The primary tissue source for endogenous glucose production is the liver and under some conditions the kidney. The clearance of glucose from the blood stream is the net consumption primarily by the brain, muscle, adipose and liver tissues. In this section, we will briefly review the regulatory contribution of each tissue in maintaining the net blood glucose concentration.

### *2.1. Liver*

The liver plays a major role in whole body glucose metabolism by maintaining a balance between glucose production and glucose storage in the form of glycogen. Approximately 80% of endogenous glucose production is accounted for by the liver and the remaining by the kidney (Gerich, 2010). In humans, the splanchnic bed (comprising the liver and gut) accounts for ~25% of glucose utilization under fasting conditions and for 35% after an oral glucose load (DeFronzo, 2004; Moore et al., 2012). When nutrients are available, as occurs after a meal, blood glucose concentrations rise. The effect of high glucose on the liver is dual. First, hyperglycemia per se promotes glucose absorption from the blood stream to be stored as glycogen. Second, it promotes insulin secretion from the pancreas that suppresses hepatic glucose production (HGP). Glucose entrance into hepatocytes is insulin-independent and is facilitated by the glucose transporter GLUT2. When nutrients become scarce, even after a few hours of fasting, the liver releases glucose to the blood by regulating the two primary glucose production metabolic pathways,