Introductory Chapter: Gluconeogenesis

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Additional information is available at the end of the chapter

Glucose, a prominent metabolic fuel in mammals, is the precursor for synthesis of all the other carbohydrates, such as glycogen, ribose, glycolipids, and glycoproteins. Blood glucose levels need to be maintained within a relatively narrow range, which is defined as the glucose homeostasis. This stable equilibrium of blood glucose levels is achieved by a balance between the dietary glucose uptake, endogenous glucose production, glucose partition, and glucose utilization. Derangement of blood glucose could cause severe outcomes. Hypoglycemia may lead to brain dysfunction, and if more severe, even death. Acute hyperglycemia sometimes reflects stressed clinical conditions such as injury or infection with poor outcomes. Chronic elevation of blood glucose causes diabetes, which results from impairment of organism glucose homeostasis.

The contribution of endogenous glucose production includes gluconeogenesis and glycogenolysis. Gluconeogenesis is the metabolic process in which glucose is produced from certain noncarbohydrate carbon substrates. These substrates include the breakdowns of proteins and lipids such as amino acids, lactate, and glycerol. Liver and kidney are two important tissues of gluconeogenesis, which are responsible for maintenance of normal blood glucose level in the fasting state or starvation. Although small intestine also expresses the key gluconeogenic enzymes, it is still not clear whether this organ produces glucose in the fasting state. Insulin and glucagon are two counteracting hormones critical for the regulation of gluconeogenesis. These hormones can act acutely to alter the enzyme activity or chronically through gene expression. In addition to the peripheral targets, these hormones have been recently identified to also act through the hypothalamic neurons. Hypothalamic centers involved in the control of endogenous glucose production can constantly sense fuel availability by integrating inputs from circulating nutrients and gluconeogenic hormones. In response to these peripheral signals, the hypothalamus sends out efferent impulses to alter hepatic gluconeogenesis, thus keeping blood glucose levels in the normal range. Disruption of this intricate neural control may contribute to defects of glucose homeostasis and insulin resistance in type 2 diabetes and obesity [1].

This book aims to provide an overview on the gluconeogenesis, its regulation, and impact on the glucose homeostasis. The first chapter addresses the fundamental process by which glucose homeostasis is maintained. In this chapter, mechanisms by which glucose is transported into cells are first reviewed. The first rate-limiting step of glucose metabolism is the transport of monosaccharides into cells. This is achieved by three classes of glucose transporters: the facilitative glucose transporters, the sodium-glucose co-transporters, and sweet family, also known as PQ-loop, Saliava or MtN3 family. The second section provides a comprehensive summary on the critical biochemical processes of glucose metabolism within cells with focus on gluconeogenesis. The roles of distinct tissues such as pancreas, liver, kidney, and hypothalamic-pituitary axis in the glucose homeostasis are fully discussed in the last section. In addition to the classical hormones, insulin and glucagon, pancreatic islet cells also secrete somatostatin, amylin, and pancreatic polypeptide (PP). All these hormones are critically involved in the regulation of glucose metabolism in three major metabolic tissues including liver, adipose tissue, and skeletal muscle. Glucose transport and metabolism, in particular gluconeogenesis, in liver and kidney are comprehensively addressed. The hypothalamic-pituitary-adrenal (HPA) axis in the control of glucose homeostasis and its relation to the regulation of reproduction are reviewed at the end.

The second chapter provides a comprehensive overview on the biochemical process of gluconeogenesis in eukaryotic cells using the *Dictyostelium discoideum* as a model. This chapter opens with the introduction on the general biochemical process of gluconeogenesis in the eukaryotic cells. This is followed by an overview on how gluconeogenesis affects the developmental stages of *D. discoideum* and the differentiation process of *Myxamoebae*. Grown as single cells, *D. discoideum* develops as multicellular organisms. The metabolic pathway and its signaling regulation are similar to that presented in plants and animals. *D. discoideum* is thus the best biological system to study the molecular pathways like glycolysis or gluconeogenesis relative to the mammalian system.

The third chapter provides a comprehensive review on the gut-brain-liver axis and its role in the control of glucose homeostasis. The current knowledge on the gut-brain interaction and its precise control on hepatic gluconeogenesis is provided, with focus on the gastrointestinal hormones and hypothalamic neuronal signaling. In this chapter, the gut-dorsal vagal complex-liver axis and the gut-hypothalamus-liver axis are first introduced. The molecular mechanism underlying the central neuronal regulation of hepatic gluconeogenesis is addressed. As the regulatory center for glucose homeostasis, hypothalamic neurons integrate peripheral hormone signals and nutrient levels to coordinate the hepatic glucose production. As proposed by Rojas and Schwartz [2] in the two-compartment model, the hypothalamus may thus be considered as another key organ critical for glucose homeostasis in addition to the pancreatic islets.

The fourth chapter addresses the new mathematical model for monitoring and prediction of blood glucose. It provides a comprehensive overview on the mathematical modeling of blood glucose dynamics, development of blood glucose prediction algorithm, and its approbation on clinical data. This predictive algorithm is based on the Sigma-model. It estimates the difference between theoretical and experimental tracks with possibility of further correction. Blood

glucose prediction algorithm allows for detection of incorrect measurements and correction spikes on blood glucose track, allowing patients to avoid incorrect insulin infusion or glucose intake. In addition, the algorithm can alert about closed-loop blood glucose control system failures. It allows patients to detect damage or cross-clamping of insulin pump infusion set and actualize meal data.

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