Central nervous system and glucose homeostasis

Juan Ding

Abstract

Type 2 diabetes (T2D) is closely associated with obesity. Obesity features an abnormality in energy balance with excess energy stored in fat tissues. In T2D, the ability to regulate glucose homeostasis is compromised resulting in hyperglycemia (high levels of blood glucose). Central nervous system (CNS) plays an important role in energy and glucose homeostasis [1]. In normal situations, the neurons in the arcuate nucleus (ARC) of hypothalamus are able to sense the nutrient levels (such as glucose and lipids) as well as hormonal signals (such as insulin and leptin), and ultimately control eating behavior and hepatic glucose production [1].

Mechanism of this sensing involves, among others, ATP-sensitive potassium channels (K\textsubscript{ATP} channels) [1]. The K\textsubscript{ATP} channel is expressed in both neurons and beta cells. It is composed of a homo tetramer of two subunits: sulfonylurea receptor 1 (SUR1), a member of ATP-binding cassette (ABC) super-family, and a potassium inward rectifier subunit KIR6.2 [2]. Glucose itself serves as a signal to activate neuronal K\textsubscript{ATP} channels leading to decreased hepatic glucose production [3]. Insulin can also activate K\textsubscript{ATP} channels in the hypothalamus [4]. Raising levels of long chain fatty acid-Coenzyme A (LCFA-CoA) in the hypothalamus as a result of either high levels of plasma free fatty acids (FFAs) [5] or inhibition of hypothalamic fatty acid oxidation [6] also activate K\textsubscript{ATP}, resulting in reduced liver glucose production.

Importantly, pharmacological activation of hypothalamic K\textsubscript{ATP} channels without nutrient or hormonal changes leads to lowered blood glucose levels by inhibiting hepatic glucose production. On the other hand, blocking the K\textsubscript{ATP} channels in the brain abolishes the hormonal and nutrient effects on hepatic glucose production. Further, mice lacking SUR1 subunit of K\textsubscript{ATP} are also resistant to these inhibitory effects. The brain regulation of hepatic glucose production acts through efferent vagus nerve because surgical resection of the hepatic branch of the vagus nerve abolishes the inhibiting effect on liver glucose production [4-6].
Interestingly, upper intestinal lipids can activate an intestine-brain-liver neural axis to inhibit glucose production [7]. Thus, neuronal regulation of glucose homeostasis involves both direct nutrient/hormone sensing of CNS neurons as well as input from peripheral autonomic sensory neurons. The integrated signal converges to activate $K_{ATP}$ channels of specific hypothalamic neurons that ultimately lead to reduced liver glucose production via output vagus nerve.

References


