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Commentary

Hypothalamic AMP-activated Kinase Regulates Glucose-stimulated Insulin Secretion

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Hypothalamic AMP-activated protein kinase (AMPK) is one of the central regulators in energy metabolism. It was originally found that inhibition of hypothalamic AMPK by insulin, leptin or alpha-lipoic acid decreases food intake (Minokoshi et al., 2004; Kim et al., 2004), and consequent studies have found that this mediates triiodothyronine's effect on thermogenesis in brown adipose tissue (Lopez et al., 2010). AMPK is an enzyme activated during low cellular energy charge, and AMPK in the hypothalamus may sense whole body energy status (Kim et al., 2004).

Glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells is biphasic, and suppression of the first-phase GSIS is one of the most characteristic findings of β-cell dysfunction in type 2 diabetes (Basu et al., 1996; Weyer et al., 1999; Seino et al., 2011). Consistently, decreased early insulin response is associated with post-prandial hyperglycemia (Basu et al., 1996), and improvement in the first-phase GSIS has been proposed as a strategy for better glycemic control in type 2 diabetes. However, at present, little is known on the mechanism underlying diabetes-related dysregulation of first-phase GSIS.

In this issue of *EBioMedicine*, Kume and colleagues have identified a novel role of hypothalamic AMPK in the regulation of first-phase GSIS in the pancreas (Kume et al., 2016). They focused on the relationship between fasting-dependent decrease in the first-phase GSIS and β-cell dysfunction in type 2 diabetes. Their study used human- and animal-based experiments to reveal that prolonged fasting reduces first-phase GSIS by signaling via the brain-sympathetic nerve-β-cell axis. Reduced first-phase GSIS after prolonged fasting decreased and increased glucose redistribution to peripheral tissues and brain, respectively, thereby increasing the possibility to maintain glucose supply to the brain at time of refeeding after prolonged fasting. Interestingly, excitation of the hypothalamic AMPK-β-cell neural axis impaired first-phase GSIS in both fasted rats and a rat model of type 2 diabetes. Furthermore, surgical denervation of the pancreas dramatically improved first-phase GSIS, glycemic control, and β-cell survival in a murine diabetic model.

Decreased first-phase GSIS may be a common insulin secretion pattern during times of scarcity and type 2 diabetes. In this study, the authors suggested an interesting hypothesis that beta cells in diabetic individuals mistakenly sense that they are under conditions that mimic prolonged fasting. This so-called "starvation diabetes" was first observed in 1960s (Unger et al., 1963), and Kume et al. have now solidified the notion that starvation mechanism is closely associated with the pathogenesis of type 2 diabetes (Kume et al., 2016). During evolution, mammals may have developed a well-organized system to regulate blood glucose levels and to avoid serious hypoglycemia during starvation. These mechanisms may be involved in the pathogenesis of type 2 diabetes. Therefore, identifying the mechanism(s) underlying starvation diabetes may facilitate a better understanding of type 2 diabetes.

In the context of translation to clinical practice, the authors have highlighted the therapeutic potency of pancreatic denervation for type 2 diabetes (Kume et al., 2016). Surprisingly, this surgical approach not only improved glycemic control but also prevented future β-cell loss. This suggests a novel possibility that hyperactivation of hypothalamic AMPK by fasting leads to both acute and chronic impairment of pancreatic β cell function, even though the mechanism of diabetes prevention by pancreatic denervation remains to be determined.

It also remains to be determined whether the present findings can translate to the management of type 2 diabetes. Interestingly, similar approaches are currently approved as therapeutic interventions in other diseases, including bariatric surgery for severe obesity (Mingrone et al., 2012) and renal denervation for hypertension (Esler et al., 2010). If pancreatic denervation can be technically applied to human type 2 diabetic patients, this surgical approach may become a novel therapeutic strategy to improve glycemic control by improving β-cell function and survival. Again, the increasing incidence of type 2 diabetes is a global public health problem. We hope that we will be able to combat type 2 diabetes by continued efforts to fully understand disease pathogenesis.

Disclosure

The author declared no conflicts of interest.

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