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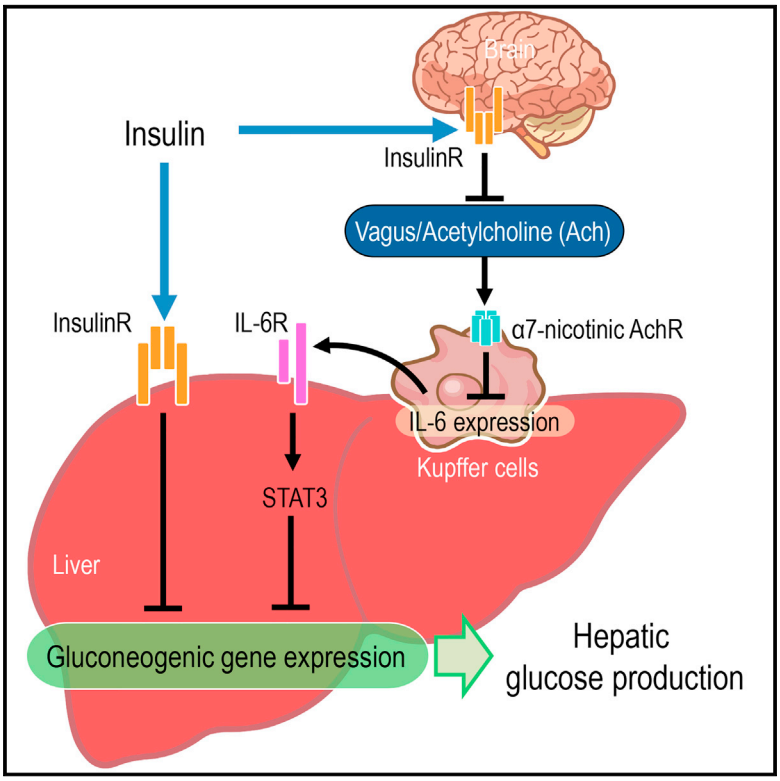
Central Insulin Action Activates Kupffer Cells by Suppressing Hepatic Vagal Activation via the Nicotinic Alpha 7 Acetylcholine Receptor

Graphical Abstract



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In Brief

In this paper, Kimura et al. show a mechanism of the central insulin-mediated hepatic response, where central insulin action—known to suppress hepatic glucose production via hepatic IL-6/STAT3 activation—mitigates the α7-nAchR-dependent downregulation of IL-6 expression in Kupffer cells by the vagus nerve.

Highlights

- Central insulin action suppresses activity of the hepatic branches of the vagus nerve
- Central insulin action activates hepatic STAT3 by mitigating nAchR suppression
- α7-nAchR-mediated control of Kupffer cells is needed for the brain hepatic response
- Obesity impedes central insulin-dependent regulation of vagus nerve activity

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Central Insulin Action Activates Kupffer Cells by Suppressing Hepatic Vagal Activation via the Nicotinic Alpha 7 Acetylcholine Receptor

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SUMMARY

Central insulin action activates hepatic IL-6/STAT3 signaling, which suppresses the gene expression of hepatic gluconeogenic enzymes. The vagus nerve plays an important role in this centrally mediated hepatic response; however, the precise mechanism underlying this brain-liver interaction is unclear. Here, we present our findings that the vagus nerve suppresses hepatic IL-6/STAT3 signaling via α7-nicotinic acetylcholine receptors (α7-nAchR) on Kupffer cells, and that central insulin action activates hepatic IL-6/STAT3 signaling by suppressing vagal activity. Indeed, central insulin-mediated hepatic IL-6/STAT3 activation and gluconeogenic gene suppression were impeded in mice with hepatic vagotomy, pharmacological cholinergic blockade, or α7-nAchR deficiency. In high-fat diet-induced obese and insulin-resistant mice, control of the vagus nerve by central insulin action was disturbed, inducing a persistent increase of inflammatory cytokines. These findings suggest that dysregulation of the α7-nAchR-mediated control of Kupffer cells by central insulin action may affect the pathogenesis of chronic hepatic inflammation in obesity.

INTRODUCTION

Insulin directly controls glucose metabolism in various target organs such as skeletal muscle, adipose tissue, and the liver, while also acting indirectly on the CNS to regulate glucose/energy metabolism (Plum et al., 2006; Schwartz et al., 2013). In fact, brain-specific insulin receptor knockout mice display insulin resistance, in addition to increased food intake, body weight, and obesity (Brüning et al., 2000). Various studies have indicated that central insulin action reduces hepatic glucose production (HGP), especially in rodents (Obici et al., 2002). Increased circulating levels of insulin result in the activation of hypothalamic insulin receptor/phosphatidylinositol 3-kinase (PI3-K) signaling, leading to the suppression of HGP via hypothalamic ATP-dependent potassium channels, which is activated by PI3-K (Carey et al., 2013; Prodi and Obici, 2006). Indeed, the suppression of HGP using the hyperinsulinemic-euglycemic clamp technique is impeded by insulin receptor deficiency, insulin receptor knockdown, and PI3-K inhibition in the hypothalamus (Inoue et al., 2006; Obici et al., 2002). Moreover, intracerebroventricular (ICV) administration of insulin and ATP-dependent potassium