Hepatocyte Adenosine Kinase Aggravates the Effect of Ketogenic Diet on Increasing Body Weight and Metabolic Dysregulation in Mice

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Abstract

Adenosine kinase (ADK) catalyzes the phosphorylation of adenosine to adenosine monophosphate. Hepatocyte-specific ADK overexpression (Hep-ADK^{Tg}) has been shown to increase adiposity and systemic insulin resistance in mice. While the ketogenic diet (KD) is often utilized for weight management, its efficacy remains controversial across different models. This study investigated the metabolic impact of long-term KD on Hep-ADK^{Tg} mice in two distinct phases: Study 1 focused on young mice before obesity onset (5-6 weeks old), and Study 2 targeted mid-aged mice with preexisting obesity (7 months old). In Study 1, seven months of KD feeding induced significantly greater weight gain and glucose intolerance in both Hep-ADK^{Tg} and wild-type (WT) mice compared to low-fat diet (LFD) controls. Notably, this obesogenic response was substantially more severe in the Hep-ADK^{Tg} group. In Study 2, the detrimental effects were further exacerbated, with KD-fed Hep-ADK^{Tg} mice exhibiting maximal weight gain and peak severity of hepatic steatosis and inflammation. In conclusion, long-term KD feeding promotes weight gain and exacerbates metabolic dysfunction in both WT and Hep-ADK^{Tg} mice. These deleterious effects are significantly amplified by ADK-driven obesity, indicating that genetic background and preexisting metabolic status are critical determinants of KD-mediated physiological outcomes.

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