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Article

p-Coumaric Acid Enhances Hypothalamic Leptin Signaling and Glucose Homeostasis in Mice via Differential Effects on AMPK Activation

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Abstract: AMP-activated protein kinase (AMPK) plays a crucial role in the regulation of energy homeostasis in both peripheral metabolic organs and the central nervous system. Recent studies indicated that *p*-Coumaric acid (CA), a hydroxycinnamic phenolic acid, potentially activated the peripheral AMPK pathway to exert beneficial effects on glucose metabolism in vitro. However, CA's actions on central AMPK activity and whole-body glucose homeostasis have not yet been investigated. Here, we reported that CA exhibited different effects on peripheral and central AMPK activation both in vitro and in vivo. Specifically, while CA treatment promoted hepatic AMPK activation, it showed an inhibitory effect on hypothalamic AMPK activity possibly by activating the S6 kinase. Furthermore, CA treatment enhanced hypothalamic leptin sensitivity, resulting in increased proopiomelanocortin (POMC) expression, decreased agouti-related peptide (AgRP) expression, and reduced daily food intake. Overall, CA treatment improved blood glucose control, glucose tolerance, and insulin sensitivity. Together, these results suggested that CA treatment enhanced hypothalamic leptin signaling and whole-body glucose homeostasis, possibly via its differential effects on AMPK activation.

Keywords: *p*-Coumaric acid; AMPK; leptin signaling; glucose homeostasis; HFD-induced obesity

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1. Introduction

AMP-activated protein kinase (AMPK) is a cellular energy sensor that plays a crucial role in the regulation of whole-body energy balance [1]. Activation of AMPK is mediated via several mechanisms but requires phosphorylation of Thr172 residue in the catalytic α-subunit [1]. It is well known that AMPK activation in peripheral metabolic organs such as liver, muscle, and adipose tissues shifts the cellular metabolism from anabolic to catabolic processes, resulting in many favorable effects on glucose and lipid metabolism and insulin sensitivity [1,2]. However, in the central nervous system, activation of hypothalamic AMPK was shown to promote feeding and weight gain whereas inhibition of hypothalamic AMPK activity enhanced hypophagia and weight loss, as well as lowering glucose production [3–5]. Modulation of AMPK activity in the hypothalamus was also shown to mediate leptin's effects on food intake and whole-body energy metabolism [3,6]. The pleiotropic actions of AMPK in metabolic health make it a promising therapeutic target in the treatment of obesity and metabolic diseases [7–9].