

# Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics

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Ketone body metabolism is a central node in physiological homeostasis. In this review, we discuss how ketones serve discrete fine-tuning metabolic roles that optimize organ and organism performance in varying nutrient states and protect from inflammation and injury in multiple organ systems. Traditionally viewed as metabolic substrates enlisted only in carbohydrate restriction, observations underscore the importance of ketone bodies as vital metabolic and signaling mediators when carbohydrates are abundant. Complementing a repertoire of known therapeutic options for diseases of the nervous system, prospective roles for ketone bodies in cancer have arisen, as have intriguing protective roles in heart and liver, opening therapeutic options in obesity-related and cardiovascular disease. Controversies in ketone metabolism and signaling are discussed to reconcile classical dogma with contemporary observations.

Ketone bodies are a vital alternative metabolic fuel source for all domains of life, eukarya, bacteria, and archaea (Aneja et al., 2002; Cahill, 2006; Krishnakumar et al., 2008). Ketone body

and modulators of inflammation and oxidative stress. In this review, we provide both classical and modern views of the pleiotropic roles of ketone bodies and their metabolism.