

GPCRs for ketone bodies and energy homeostasisJunki Miyamoto^{1,2}¹*Tokyo University of Agriculture and Technology*, ²*AMED-CREST*

Ketone bodies such as β -hydroxybutyrate and acetoacetate are important alternative energy sources under nutrient deprivation. Ketone bodies are produced in liver during starvation, exercise, type I diabetes or feeding low-carbohydrate, medium-chain triglyceride diets, and have been shown to affect cellular signaling including the activity of histone deacetylases (HDACs) and G-protein coupled receptors (GPCRs). For example, β -hydroxybutyrate also acts as a signaling molecule via specific GPCRs such as GPR109A and GPR41 which are expressed in various tissues and involved in a variety of metabolic processes. However, the specific GPCRs for acetoacetate and its physiological functions remain unclear. Here, we identified acetoacetate as an endogenous agonist for a specific GPCR by ligand screening in heterologous expression system. Acetoacetate-GPCR signaling maintains energy homeostasis through lipid metabolism under ketogenic conditions. These observations provide insight into the role of ketone bodies in energy metabolism and highlight their therapeutic potential for ketogenic metabolic disorders.