2022

γ-Glutamyl Valine, Found in Dry Edible Beans, Is Anti-diabetic in db/db Mice

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Objectives: Dietary γ-glutamyl peptides (γ-GPs) found in dry edible beans exhibit biological activities (antioxidant, anti-inflammatory) with potential benefits against chronic metabolic disorders. γ-GPs are responsible for the desirable Kokumi flavor through allosteric activation of the Calcium Sensing Receptor (CaSR) present in multiple mammalian tissues. In this study, we investigated the metabolic effects of γ-glutamyl valine (γ-EV) in diabetic obese mice.

Methods: Four-weeks old male *db/db* mice (BKS.Cg-*Dock7*^{m} +/+ *Lepr*^{db}/J) were fed AIN-93G diet *ad libitum* and given water with or without γ-EV (500 mg/kg body weight) for 3 weeks. After 3 weeks of intervention, blood, intestine and liver were collected to determine blood glucose, blood plasma γ-EV concentrations (LC-MS/MS), alanine aminotransferase (ALT) activity, jejunum and liver transcriptomes (RNA-Seq), liver protein expression (Western blot), and liver glycogen content.

Results: Mice given γ-EV had higher weight gain (45%, $p < 0.001$, $n = 8$), lower food intake (21%, $p < 0.0001$), and better food efficiency (79%, $p < 0.0001$) than their control counterparts. γ-EV blood concentrations reached 2.07 $\pm$ 0.56 μM. Blood glucose levels decreased (29%, $p < 0.01$) and urination was markedly improved. The hepatosomatic index increased (66%, $p < 0.0001$); however, blood ALT activity was not significantly changed. RNA-Seq analysis revealed 147 jejunal genes and 1308 liver genes were differentially expressed due to γ-EV intake, 26 of these genes were common to these tissues. The top 3 GO categories affected by γ-EV in jejunum were fatty acid metabolic process (17/193 genes), lipid metabolic process (22/545 genes), and peroxisome (11/136 genes); and in liver, the top 3 GO categories were oxidoreductase activity (104/686 genes), lipid metabolic process (79/545 genes), and iron ion binding (43/185 genes). Hepatic AMP-activated protein kinase (p-AMPKα, Thr172) abundance, a major cellular regulator of lipid and glucose metabolism, increased (86%, $p < 0.05$), and liver glycogen decreased (79%, $p < 0.0001$) in the treatment group suggesting γ-EV induced catabolism.

Conclusions: γ-EV improved the diabetic condition of *db/db* mice via modulation of glucose and lipid metabolism.

Funding Sources: Funding was provided by the University of Nebraska-Lincoln Collaboration Initiative and the Nebraska Dry Bean Commission.

Curr Dev Nutr. 2022 Jun; 6(Suppl 1): 339. Published online 2022 Jun 14.
doi: 10.1093/cdn/nzac053.080
PMCID: PMC9193758