News Release

Soy protein β-conglycinin ameliorates pressure overload-induced heart failure by increasing short-chain fatty acid (SCFA)-producing gut microbiota and intestinal SCFAs

Key Points

- The progression of pressure-overloaded heart failure in a mouse model was ameliorated by feeding a diet containing β-conglycinin (β-CG), a functional soy protein with anti-obesity effects, by modulating intestinal microbiota.
- Feeding β-CG increased three types of SCFA-producing bacteria and intestinal concentrations of SCFAs (acetic acid, butyric acid and propionic acid).
- Oral administration of sodium propionate indeed suppressed the heart failure progression, as did β-CG feeding.

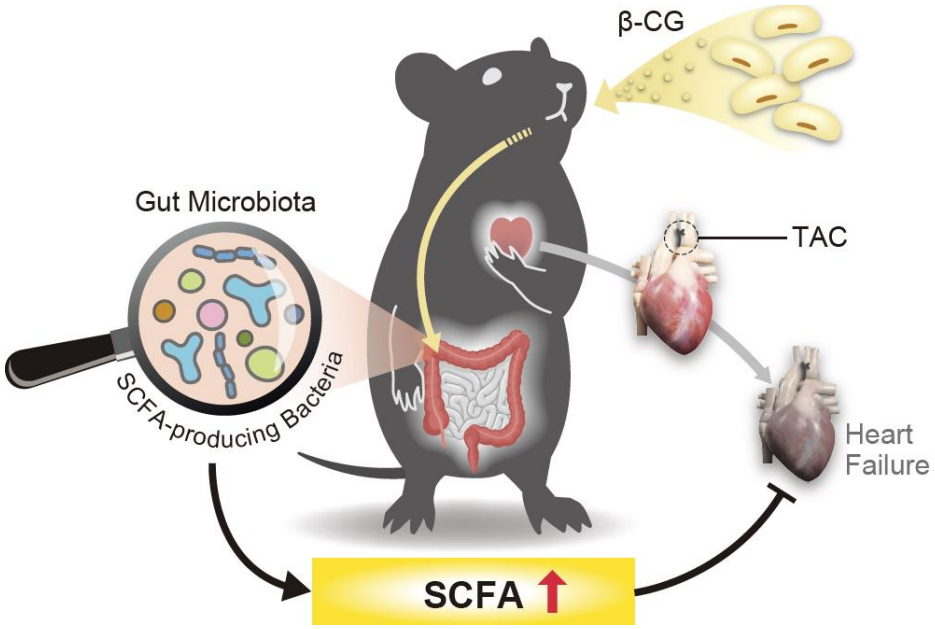
Summary

Background and Aims : Soybeans and their ingredients have antioxidant and anti-inflammatory effects on cardiovascular diseases. β-Conglycinin (β-CG), a major constituent of soy proteins, is protective against obesity, hypertension, and chronic kidney disease, but its effects on heart failure remain to be elucidated. We tested the effects of β-CG on left ventricular (LV) remodeling in pressure overload-induced heart failure.

Methods: A transverse aortic constriction (TAC)-induced pressure overload was applied to the heart in 7-week-old C57BL6 male mice that were treated with β-CG, N-acetyl glucosamine (GlcNAc), or sodium propionate. Gut microbiota was analyzed by 16S rRNA sequencing. Fecal short chain fatty acids (SCFAs) were quantified by gas chromatograph-mass spectrometry (GC-MS). The effects of oral antibiotics were examined in β-CG-fed mice.

Results: β-CG ameliorated impaired cardiac contractions, cardiac hypertrophy, and myocardial fibrosis in TAC-operated mice. As β-CG is a highly glycosylated protein, we examined the effects of GlcNAc. GlcNAc had similar but less efficient effects on LV remodeling compared to β-CG. β-CG increased three major SCFA-producing intestinal bacteria, as well as fecal concentrations of SCFAs, in sham- and TAC-operated mice. Oral administration of antibiotics nullified the effects of β-CG in TAC-operated mice by markedly reducing SCFA-producing intestinal bacteria and fecal SCFAs. In contrast, oral administration of sodium propionate, one of SCFAs, ameliorated LV remodeling in TAC-operated mice to a similar extent as β-CG.

Conclusions: β-CG was protective against TAC-induced LV remodeling, which was likely to be mediated by increased SCFA-producing gut microbiota and increased intestinal SCFAs. Modified β-CG and/or derivatives arising from β-CG are expected to be developed as prophylactic and/or therapeutic agents to ameliorate devastating symptoms in heart failure.



Graphical summary. Ingestion of β-conglycinin (β-CG), a major constituent of soy proteins, increases short-chain fatty acid (SCFA)-producing intestinal bacteria and intestinal SCFA productions. SCFA prevents the development and progression of heart failure caused by transverse aorta constriction (TAC).

Research Background

Heart failure is an intractable disease with a poor prognosis. Pathological cardiac stress based on lifestyle-related diseases such as hypertension leads to myocardial wall thickening and cardiac hypertrophy in an attempt to compensate for the load, which subsequently leads to chronic heart failure where both contractile and diastolic function are disrupted. Soy and its components have antioxidant and anti-inflammatory functions and protect against cardiovascular injury (Hagen MK et al., *Nutr Metab Cardiovasc Dis*. 2009; Qin W et al., *Br J Pharmacol*. 2015). Soy protein β-CG is known to be a functional soy component showing anti-obesity effects (Hashidume T et al., *Sci Rep*. 2016), but it remains undetermined whether β-CG has any effects on cardiovascular disease, particularly in the pathological progression of cardiac hypertrophy-heart failure.

Research Results

When a diet containing soy protein β-CG was fed as a protein source for five weeks before and after the creation of a TAC-induced pressure-loaded

heart failure model, left ventricular remodeling (cardiac dysfunction, cardiac hypertrophy and myocardial fibrosis) caused by pressure loading was significantly reduced compared to a control feeding group. To explore the underlying mechanisms of the amelioration of remodeling by β-CG, we analyzed the gut microbiota and its metabolites by 16S rRNA-seq[*3] and GC-MS, respectively. We found that β-CG feeding increased representative SCFA-producing bacteria (genera *Butyricimonas*, *Marvinbryantia*, and *Anaerotruncus*) and intestinal SCFAs, and that the abundances of some SCFA-producing bacteria, which were increased by β-CG feeding, were inversely correlated to myocardial fibrosis and myocardial fibrosis, indicating that SCFAs may directly ameliorate the left ventricular remodeling. As expected, oral administration of sodium propionate that was released in the large intestine also suppressed left ventricular remodeling as we observed in β-CG feeding. In contrast, oral administration of antibiotics abolished the cardioprotective effect of β-CG. We concluded that β-CG exerts cardioprotective effects by increasing intestinal SCFA-producing bacteria and intestinal SCFA concentrations.

Research Summary and Future Perspective

Importantly, this study shows that β-CG changes gut microbiota and shows cardioprotective effects. β-CG is (i) an indigestible soy constituent (Elisabetta D.A. et al., *Food Funct*. 2017) and (ii) a glycoprotein containing many oligomannose-type glycans. (Cheng L et al., *Food Science and Human Wellness*. 2023). This study elucidated that β-CG increases SCFAs and their producing bacteria and that oral administration of large intestine-released SCFA also has a therapeutic effect on left ventricular remodeling. However, we will still have to elucidate which domain(s) or glycan(s) constituting β-CG increases SCFA-producing intestinal bacteria. As β-CG is highly allergenic, further molecular dissection of β-CG will enable the development of a novel therapeutic agent to mitigate devastating development and progression of the heart failure.

Publication

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The patent is pending for this achievement.

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