Through β2-Adrenergic Receptors Gut Microbe Metabolite Found to Modulate Heart Disease Risk

Recent clinical studies have suggested that phenylacetylglutamine (PAGln), a novel gut microbial metabolite, can mechanistically modulate patients' risk of developing cardiovascular disease (CVD) and heart failure (HF). In a recent study, researchers examine the mechanisms involved in the association between PAGln and adverse cardiovascular outcomes.

Study

Previous studies have identified the adrenergic receptor (AR)-binding potential of PAGln, which suggests its potential role in allosteric modulation. ARs are host receptors involved in a wide range of critical metabolic, homeostatic, and cardiovascular functions across the heart, adipose tissue, neurons, and vasculature. The present study aims to verify this hypothesis and further identify the regulatory 'fine-tuning' pathways linking PAGln to CVD outcomes.

The human embryonic kidney 293 (HEK293) line was used to stably express a tetracycline transactivator (tTA)-dependent luciferase reporter (HTLA) line and their genetically modified derivatives. To evaluate the potential allosteric effects of PAGln, cells were exposed to increasing concentrations of isoproterenol and norepinephrine, both of which are β-agonists. Cyclic adenosine monophosphate (cAMP)-dose-response assays were used to evaluate the binding efficacies of native phenylalanine and PAGln to β1-HEK293, β2-HEK293, HTLA, and parental-HEK293.

To measure G protein-coupled receptor (GPCR) transduction regulation, β-arrestin2 recruitment assays using HTLA cells were conducted, and relative luminescence was measured. Subsequently, radiology and binding assays were conducted to further verify GPCR affinity and estimate its relative expression.

To non-invasively monitor the dynamic allosteric modulation of ARs following PAGln treatment, dynamic mass redistribution (DMR) studies on mutant β2-HEK293 cells were performed.

To confirm whether these in vitro biochemical assays translate to real-world outcomes, the researchers also performed cardiac muscle function tests on heart failure patients' left ventricular apical tissue and contractility tests on mouse cardiomyocytes.

Results

The cAMP assay revealed that PAGln increased the production of cAMP cells expressing β2AR receptors but not β1AR receptors. This agnostic effect was only observed during acute transient exposure of less than ten minutes.

To determine whether these interactions occur under normal physiological conditions, the β-arrestin2 recruitment assay was used to assess the effects of PAGln as a negative allosteric modulator (NAM) with or without prior exposure to β-agonists. Exposure to PAGln for 15 minutes or longer, followed by treatment with β-agonists for 10 minutes, led to similar results obtained during the cAMP assay, thus indicating that PAGln elicits NAM effects in β2AR- but not β1AR-expressing HEK293 cells.

Isometric muscle contraction assays were employed to elucidate whether PAGln impacts NAM's effects on human heart function. A significant shift in the PAGln dose-response curve was observed as compared to when PAGln was absent, thereby confirming a strong NAM effect. These findings were consistent with those observed in the murine ventricular cardiomyocyte experiments.

Conclusion

The present study presents the first evidence of a gut microbiome metabolite functioning as a NAM of a host GPCR, which suggests the substantial coevolution of the microbiome and its host.

The condition-dependent NAM effects of PAGln on human cardiovascular tissue were also observed, thus highlighting the metabolite as a partial agonist of β2AR. PAGln was further identified as an ago-allosteric modulator, a special class of allosteric modulators that independently function as agnostics but as allosteric modulators when co-incubated with other agnostics.

Taken together, these findings identify PAGln as a potential target for future anti-CVD drug discovery and the gut microbiome as an exciting opportunity for bioprospecting against chronic diseases.

Source:

https://www.news-medical.net/news/20240826/Gut-microbe-metabolite-found-to-modulate-heart-disease-risk-through-ceb22-adrenergic-receptors.aspx