Effect of Intestinal Phospholipid Metabolism Intermediates on Cardiometabolic Syndrome and Gut Microbiota in Phospholipase A_2 Deficient Mice

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Introduction

Bariatric surgery improves glucose homeostasis and decreases phospholipid metabolites (LPC, LPA, and choline) levels in humans and mice. Previous studies have shown that mice deficient in group 1B phospholipase A2 (PLA2g1b) enzyme are resistant to diabetes and obesity in response to diabetogenic high fat/high carbohydrate diet. It is possible that phospholipid metabolites produced by PLA2g1b could play a role in the development of cardiometabolic syndrome. This study examined (1) the potential of discovering which phospholipid metabolite(s) contribute(s) to the development of cardiometabolic syndrome and (2) the ability to find a novel inhibitor for PLA2g1b that could act as an intervention for the development of cardiometabolic syndrome.

Hypothesis

The bioactive lipid metabolites generated from PLA2g1b-mediated phospholipid digestion in the intestinal lumen are responsible for the adverse effects of high fat diet on cardiometabolic syndrome, through mechanism related to changes in the gut microbiome.

Methods

Wildtype and PLA2g1b$^{-/-}$ mice were fed a diabetogenic high fat/high carbohydrate diet for 16 weeks. Three PLA2g1b$^{-/-}$ groups' diet was supplemented with LPC, LPA, or choline. Metabolic parameters, lipid profile and glucose homeostasis were compared between groups. The effectiveness of PLA2 inhibitor compounds were tested against PLA2g1b enzymes. The EC50 for each compound was calculated and compared to the EC50 of methyl indoxam, a known inhibitor of PLA2g1b.

Results

Diabetogenic diet supplemented with choline but not LPC or LPA suppressed the metabolic benefits of PLA2g1b inactivation with a loss of glucose homeostasis by week 16. A trend towards a more metabolically risky gut microbiota composition was also seen in mice fed the choline supplemented diet. EC50 values of inhibitor samples # 376601 and # 489410 showed partial suppression of PLA2g1b enzyme, with EC50 values of 78.34 μM and 100.2 μM respectively.

Conclusions

The results suggest that choline may be the potential metabolite in the phospholipid pathway that contributes to the development of cardiometabolic syndrome. This experiment needs to be repeated with various doses of choline for a more rigorous study and robustness of data interpretation. This study also identified novel PLA2g1b inhibitors that may be tested for effectiveness in diabetes intervention.

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