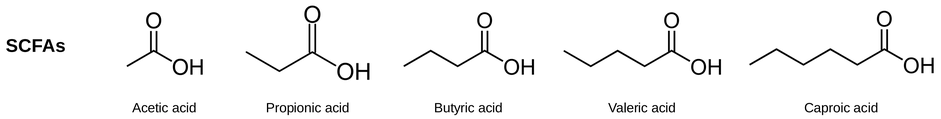
Potential of the Short Chain Fatty Acid Caproic Acid in Protection Against CVD in HIV Infection

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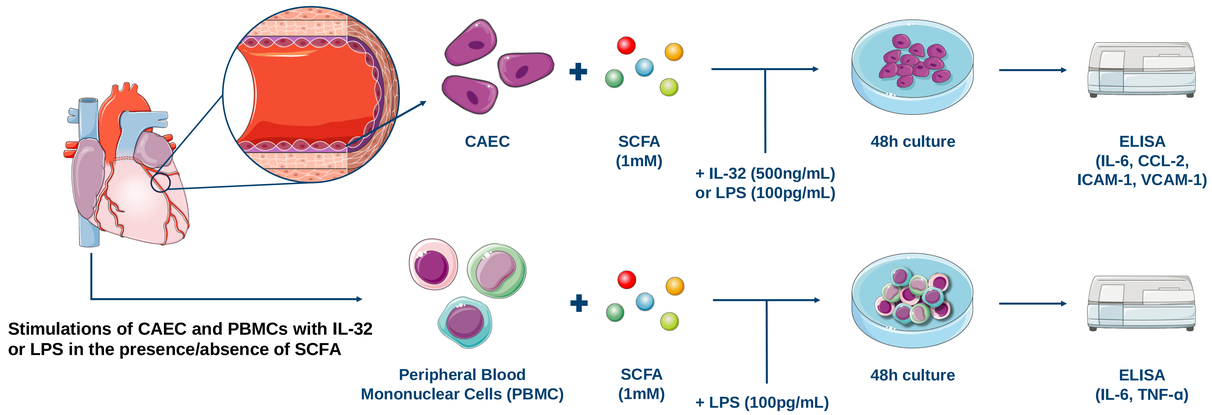
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BACKGROUND

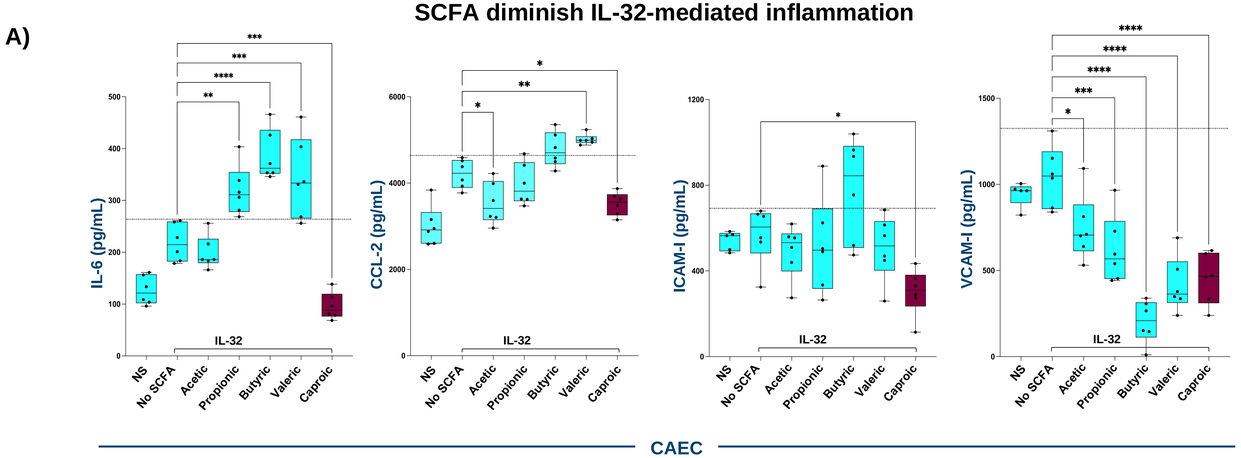


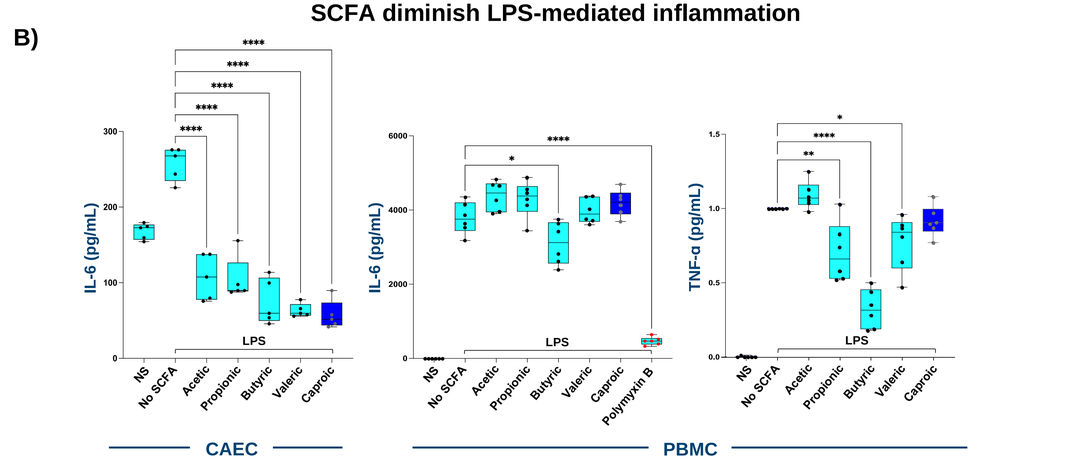
We have recently shown that gut dysbiosis in people with HIV (PWH) is associated with decreased levels of the gut metabolites short chain fatty acids (SCFAs). Deficiency of these metabolites correlated with higher inflammation, particularly in levels of the proinflammatory cytokine IL-32. We showed that IL-32 induces coronary artery endothelial cell (CAEC) inflammation and dysfunction and correlates with arterial stiffness and cardiovascular disease in PWH. In this study, we aimed to investigate the beneficial effect of the intestinal microbiota-driven SCFAs, acetate, butyrate, propionate, valerate and caproate to alleviate the IL-32-mediated CAEC dysfunction to potentially protect against CVD.

METHODS



RESULTS





A) Coronary artery endothelial cells (CAEC) stimulated with IL-32γ. In the in the absence of SCFAs, CAEC upregulate the expression of IL-6, CCL-2, ICAM-I and VCAM-I (the chronic upregulation of which is associated with endothelial cell dysfunction). CAEC pre-conditioning with SCFAs diminish the upregulation of IL-6, CCL-2, ICAM-I and VCAM-I, but with a varying potential. Caproic acid was the only SCFA being able to diminish the upregulation of all the CAEC dysfunctional markers simultaneously. **B) Activation of CAEC and PBMCs with LPS.** When LPS was used as a comparator stimulant on CAEC, all SCFAs including caproic acid, significantly diminished the upregulation of IL-6 (left panel). However, in PBMCs, the anti-inflammatory potential of caproic acid to suppress the production of IL-6 or TNF-α (middle and right panels, respectively) in response to LPS was less pronounced compared to the other candidates suggesting that caproic acid has a dominant positive effect in restoring endothelial cell functions and protecting against inflammation in cell-dependent fashion. * p<0.05, ** p<0.01, *** p<0.001.

CONCLUSIONS

Our results uncover the potential benefit of caproic acid in reversion of the endothelial cell dysfunction and inflammation mediated by either the inflammatory cytokine IL-32 or the endotoxin LPS. This effect is more selective to endothelial cells compared to peripheral blood cells. Work is in progress to understand the mechanisms involved in these selective functions including the potential differential expression of SCFA receptors in the different cell types.

ACKNOWLEDGEMENTS

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NIH National Institutes of Health
CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
the CTN CIHR Canadian HIV Trials Network
le Réseau Réseau canadien pour les essais VIH des IRSC