Changes in bioactive lipids signalling under Space conditions

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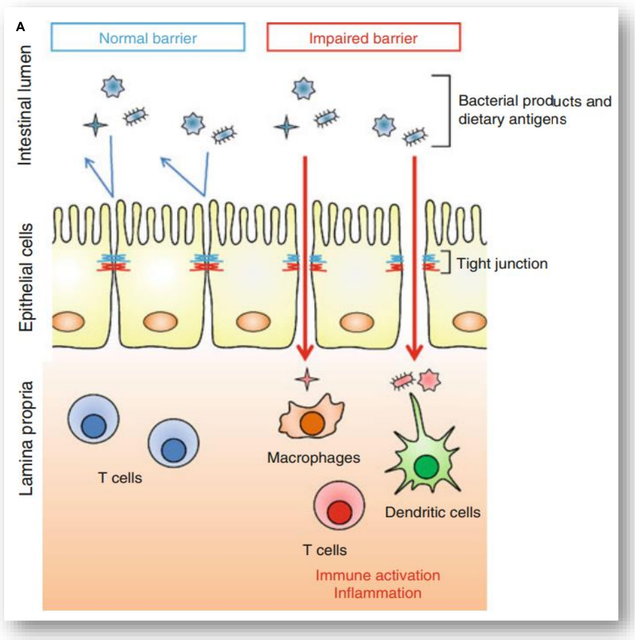
INTRODUCTION



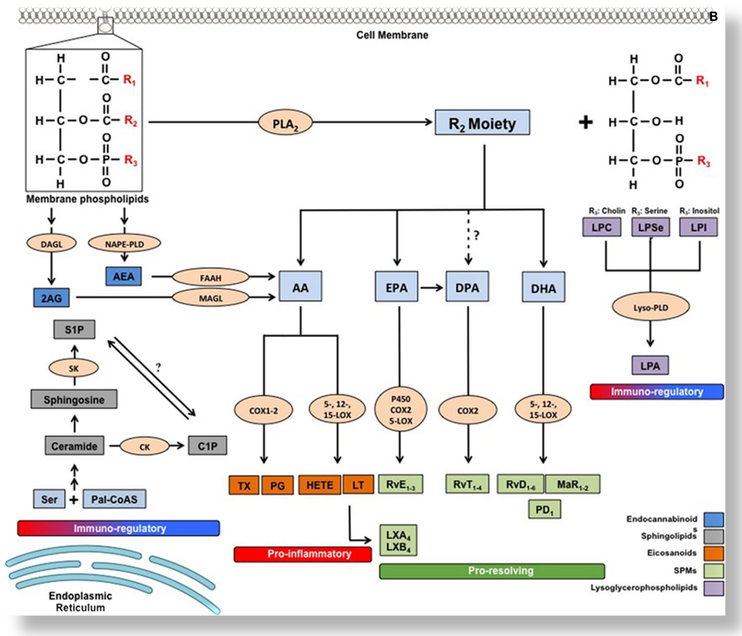
Microgravity is involved in several cellular and molecular alterations, including those associated with the immune system and gastrointestinal (GI) trait[1].

The inflammatory processes are regulated by specific endogenous lipids[2], such as the specialized pro-resolving mediators (SPMs) and endocannabinoids.

These lipids have been consistently linked to homeostasis in virtually every known disease[2], yet their involvement in Space-related disorders is scarcely known[3].

Our group has demonstrated that immune cells exposed to authentic (ROALD, RESLEM and SERiSM missions) or to simulated microgravity display altered metabolism and signalling pathways of the eCB system (ECS) [4–6].

To date, few studies have addressed the effect of microgravity on the resolution system and the ECS, nor its role on the lipid systems that control the GI homeostasis during Space travel.

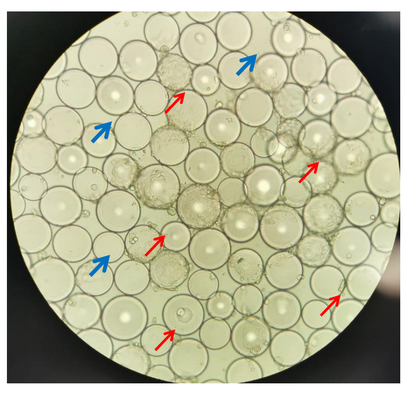


AIM OF THE STUDY

In the present study, simulated microgravity (μg) was used to assay the effect of weightlessness on the metabolism and signalling of SPMs and eCB system in human primary monocytes and on human GI cells, respectively.

METHODS

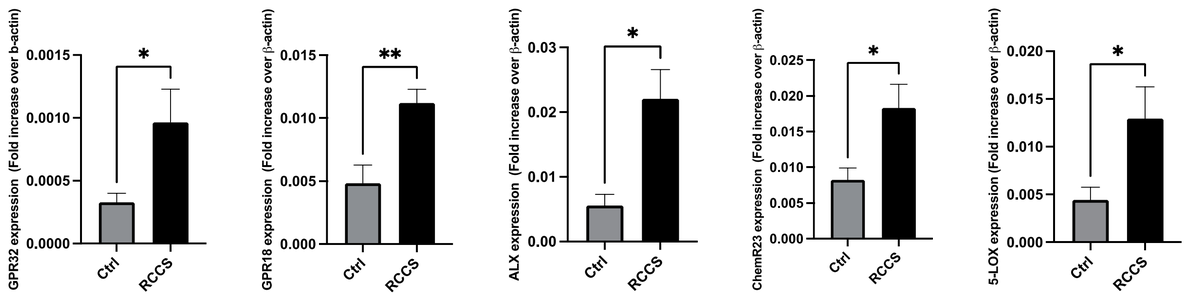
Human PBMCs (peripheral blood mononuclear cells) were isolated from human blood samples and incubated at 1xg Earth gravity or 10^{-3}xg simulated microgravity for 24h[4] by means of the Rotary Cell Culture System (RCCS) developed by NASA. Quantitative real-time PCR (qPCR) and polychromatic flow cytometry (FC) were performed to evaluate the gene and protein expression of SPMs' receptors and enzymes. The production of SPM lipids was measured by liquid chromatography-mass spectrometry (LC-MS/MS). The activity of 5-LOX was assayed by means of fluorometric kits.



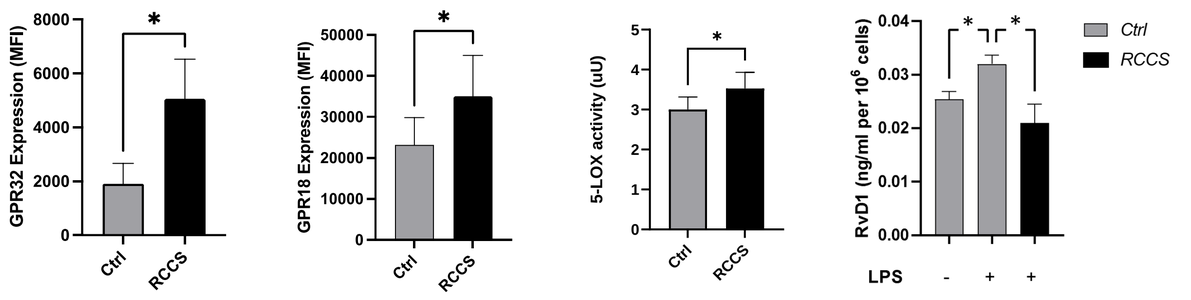
Human Caco-2 cells were chosen as a model of intestinal epithelial cells, as reported[7], and kept in adherence to Cytodex® microcarrier beads (microcarrier/cell ratio 1:20)[8] before being exposed to 1xg Earth gravity or 10^{-5}xg RCCS-simulated microgravity for 48h. Gene and protein expression of the eCB system enzymes and receptors were assayed by means of qPCR and Western Blotting.

RESULTS

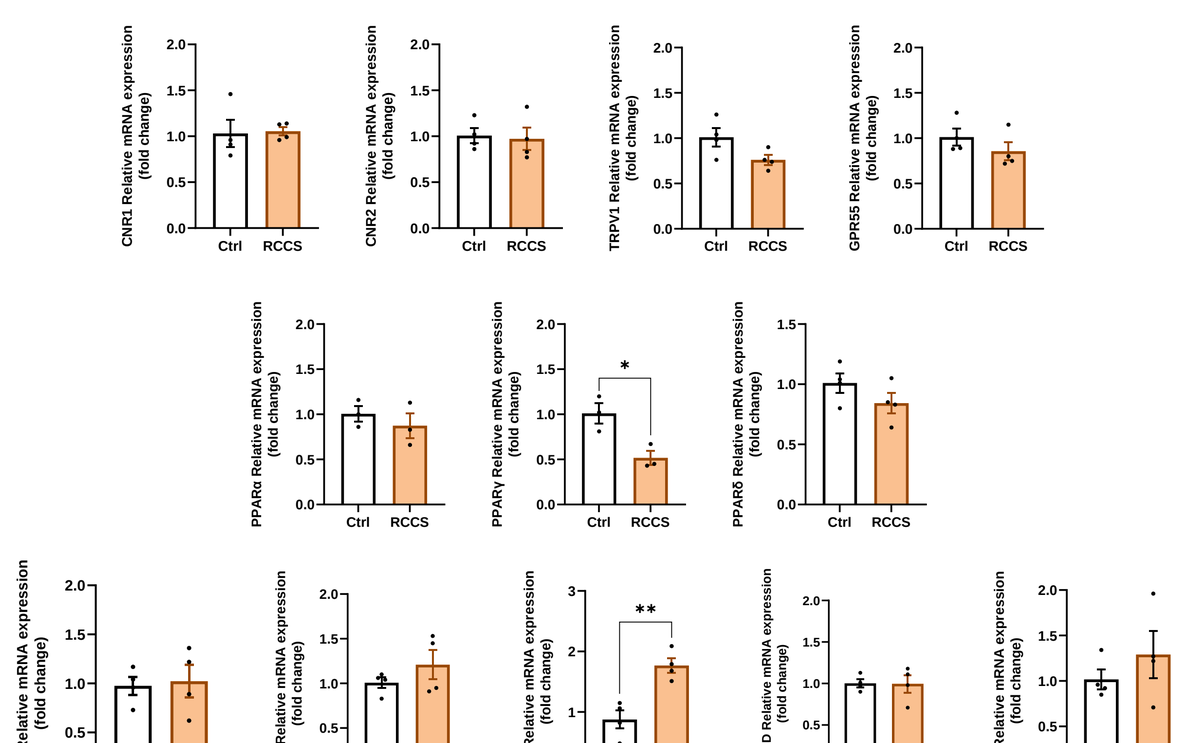
Human PBMCs that underwent 24h of simulated microgravity displayed an enhanced gene expression of pivotal SPM receptors such as GPR32, formyl peptide receptor 2 (ALX), GPR18 and Chemerin Receptor 23 (ChemR23), and of their biosynthetic enzyme 5-lipoxygenase (5-LOX) in respect to 1xg control samples.

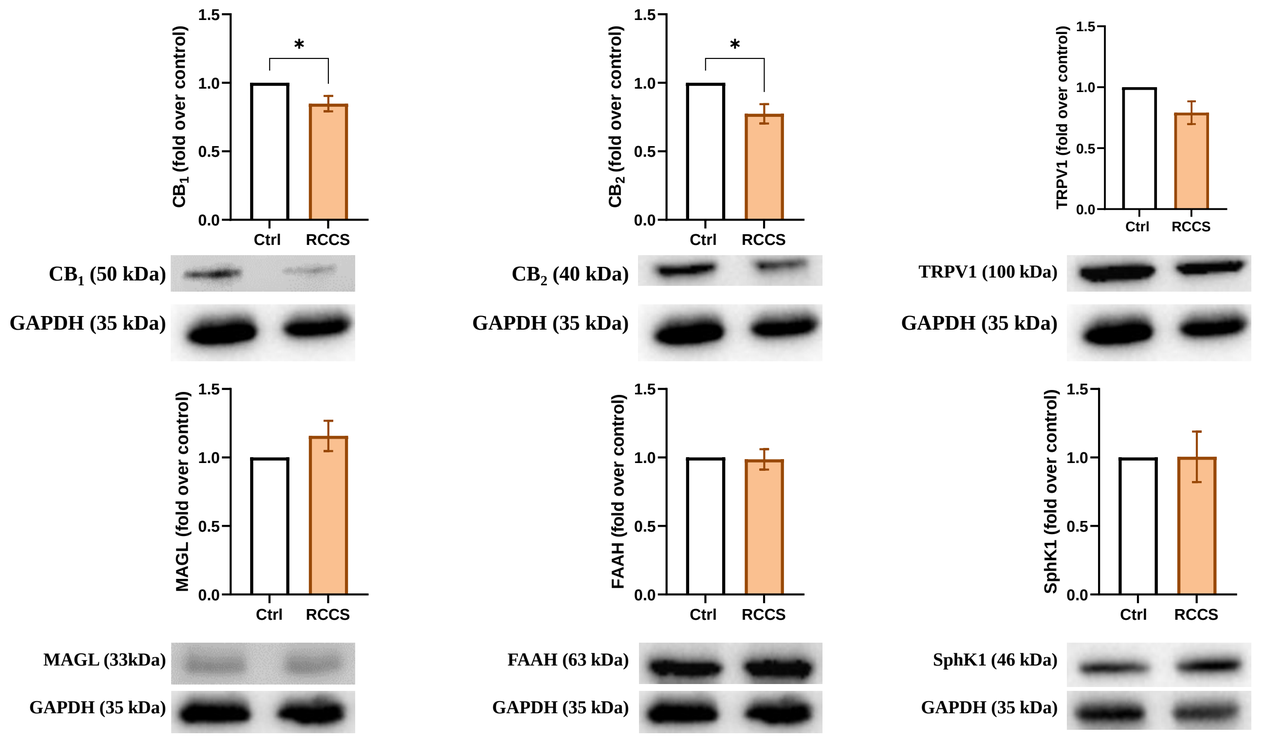


Polychromatic FC revealed that GPR32 and GPR18 underwent a significant up-regulation in CD14+ monocytes. Microgravity also elicited a significant downregulation of 5-LOX expression and activity in monocytes. At last, simulated microgravity induced an abated production of the SPM resolving (Rv) D1 in LPS-stimulated cells[9].



On the other hand, Caco-2 cells exposed to RCCS-simulated microgravity displayed a significant rearrangement in the expression of eCB-related and sphingosine-1-phosphate elements: in particular, 48h of weightlessness resulted in significantly reduced protein expression of CB_1 and CB_2 receptors, downregulation of the peroxisome proliferator-activated receptor γ (PPARγ) gene product, and upregulation of the monoacylglycerol lipase (MAGL) and sphingosine-1-phosphate receptor 1 (S1PR1) gene expression.





CONCLUSIONS

Our data show, for the first time, that short exposure to microgravity significantly affects the signalling and metabolism of SPMs in monocytes.

Space-related disorders often display unresolved inflammation, suggesting the involvement of lipids in microgravity-associated disorders.

Microgravity does indeed modulate eCB signalling even in the GI tract by decreasing the expression of crucial receptors of these bioactive lipids.

ACKNOWLEDGEMENTS

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REFERENCES