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Title
Modulation Of Inflammation And Endothelial Activation With Spaceflight Travel: Tocotrienols As Atheroprotective Agents

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The effects of immediate spaceflight travel on inflammation and endothelial activation in human endothelial cells (ECs) is not yet established. In addition, the expression of these biomarkers in revived live ECs recovered from a spaceflight travel has not been reported so far. Endothelial activation is preventable. One of the major preventive strategies is the usage of antioxidants. Tocotrienols (TCTs) is a more potent antioxidant than tocopherol (TOC). However, the role of Tocotrienol enriched mixed fraction (TEMF) and pure TCT isomers as a potential potent antiatherosclerotic agent in human ECs compared to pure α-TOC is not well established. The anti-atherosclerotic mechanism of TCTs is also unclear. The objectives of this study were to investigate (i) the effects of spaceflight travel on the protein and gene expression of inflammation and endothelial activation, nuclear factor kappa B (NFκB) and endothelial nitric oxide synthase (eNOS) in human ECs compared to ground controls, (ii) the protein and gene expression of inflammation and endothelial activation, NFκB, signal transducer and activator of transcription-3 (STAT-3) and eNOS in revived live human ECs compared to matched controls (iii) the effects of TEMF, pure TCT isomers, and α-TOC on inflammation, endothelial activation, monocytes binding activity, NFκB and eNOS, and (iv) the most potent pure TCT isomers on the inhibition of the inflammation, endothelial activation, monocytes binding activity, NFκB and eNOS biomarkers in lipopolysaccharides (LPS) stimulated human ECs. The culture medium and ECs from post-spaceflight, revived and corresponding controls were collected and measured for protein and gene expression of cytokines (IL-6 and TNF-α), adhesion molecules (ICAM-1, VCAM-1 and e-selectin), NFκB and/or STAT-3 and eNOS. Human umbilical vein endothelial cells (HUVECs) were incubated with various concentrations of TEMF, pure TCT isomers and α-TOC (0.3-10 μM) together with, lipopolysaccharides (LPS) for 16 hours. Culture medium and cells were collected and measured for the protein and gene expression of cytokines, adhesion molecules, NFκB and eNOS. The immediate post-spaceflight cells showed enhanced expression of cytokine (IL-6), adhesion molecules (ICAM-1 and VCAM-1) and NFκB compared to ground controls. Following post spaceflight, the revived cells were shown to have increased expression of IL-6, ICAM-1 and STAT-3. TEMF and pure TCT isomers reduce IL-6, ICAM-1, VCAM-1, e-selectin, monocytes binding activity, NFκB and induce eNOS expression. Area under the analysis revealed that pure TCT, particularly γ- and δ- isomers have better reduction of inflammation and endothelial activation and greater eNOS increment than TEMF. Delta (δ)-TCT is the most potent TCT isomers in terms of as an atheroprotective agent. Spaceflight travel leads to enhanced inflammation and endothelial activation and these remain elevated even after 3 months post spaceflight travel. This study provided a better understanding on the modulation of inflammation and endothelial activation associated with space travel and may direct future studies in the prevention of atherosclerosis in space travel. TEMF and pure TCT isomers exhibit anti-atherosclerotic properties with great potential as atheroprotective agents. The possible pathway for its anti-atherosclerotic activity is through the NFκB deactivation. α-TOC has inhibitory effects on the antiatherosclerotic properties of TCTs in TEMF.