

Cardiovascular Physiology

Inflammation induced disruption in Circadian Rhythm in Pulmonary Endothelial cells is modulated via reactive oxygen species

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Introduction: While the circadian clock has been characterized in systemic blood vessels and well established to contribute to various inflammatory pathologies associated with the endothelium, the mechanisms of circadian control of endothelial inflammation specifically in pulmonary inflammation is not known. We hypothesized that the pulmonary vasculature is under circadian control and that this rhythm is disrupted by inflammatory stimuli via redox mediated processes.

Objective: To determine the possible relationship between the inflammation induced disruption in Circadian Rhythm in pulmonary endothelial cells and reactive oxygen species.

Material and Methods: Circadian rhythms were monitored in pulmonary artery segments and endothelial cells isolated from mPer2luciferase transgenic mice in presence of an inflammatory stimuli (LPS). Reactive oxygen species (ROS) production in LPS treated cells was measured by fluorescence microscopy using the cell permeant dye CellROX Green.

Results: The circadian rhythm of the pulmonary endothelium was disrupted by LPS. To identify the mechanism of this disruption, ROS production in these cells was monitored. At 3 h post LPS treatment, we observed a >3 fold increase in ROS production which further increased to 6 fold by 36 h and returned to baseline values at 72 h. ROS was inhibited by pretreating the cells with the NADPH oxidase 2 (NOX2) inhibitor DPI. Addition of DPI, prior to LPS pretreatment also restored the circadian rhythmicity of the pulmonary endothelium.

Conclusions: Pro-inflammatory stimuli can disrupt circadian rhythms in the pulmonary endothelium via NOX2 regulated ROS signaling. We speculate that under inflammatory conditions disrupted circadian rhythms in the pulmonary vascular endothelium contributes to worsening outcomes.

Keywords: circadian rhythm, pulmonary endotelial cells, reactive oxygen species.