Public Abstract
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Title:CHLORINATED LIPID INDUCE INFLAMMATORY RESPONSES IN THE MICROCIRCULATION

Previous studies from our research group have shown that chlorinated lipid, generated from the neutrophil-myeloperoxidase (MPO) system, are elevated in a rat sepsis model as well as in plasma of septic patients. Other work reported in multiple experimental studies and human trials have shown that microcirculatory dysfunction is a hallmark of sepsis. However, whether and how chlorinated lipid contribute to microcirculatory dysfunction are still unclear. In the current study, we hypothesized that compared to non-chlorinated lipid, chlorinated lipid could elicit inflammatory responses in the microcirculation.
To test this postulate, a specific rat intravital model was developed. Briefly, male Sprague Dawley rats (250-300g) were randomly divided into 4 groups: 2-chloropalmitic acid (2-ClPA) group, 2-chloropalmitaldehyde (2-ClHDA) group, non-chlorinated palmitic acid (PA) group and palmitaldehyde (HDA) group (n=6). Rat mesenteries were exteriorized and superfused with 10 ?M of 2-ClPA or 2-ClHDA, respectively. Equimolar concentrations of PA and HDA were applied as controls. Via use of our intravital microscopic approach, the indicators of microcirculatory dysfunction, leukocyte-endothelial interactions (leukocyte rolling and adhesion), mast cell degranulation, reactive oxygen species (ROS) production, and albumin leakage were evaluated at 0 min (baseline), 20 min, 50 min and 80 min after the initiation of lipid superfusion, respectively. At the end of experiments, rats were sacrificed and the jejunum was collected. MPO expression from granulocytes of the jejunum was assessed by a fluorescence assay and immunohistochemistry (IHC) staining.
Results of this study showed: (1) In the PA group, very few rolling and adhesive leukocytes were detected, while in the 2-ClPA treated group, there was a significant increase in rolling and adhesive leukocytes. At all the time points examined, 2-ClPA produced significant increases in mast cell degranulation, ROS production and albumin leakage, compared with PA. (2) In the HDA group, no increase in leukocyte rolling and adhesion were observed, while 2-ClHDA produced an increase in leukocyte rolling but not stationary adhesion. HDA produced a time-dependent increase in mast cell degranulation, but this was lower than that seen in response to 2-ClHDA. ROS production and albumin leakage were significantly lower in response to HDA than with 2-ClHDA. (3) MPO expression in rat jejunum was almost 2 times higher in 2-ClPA and 2-ClHDA treated groups compared with PA and HDA groups, respectively. Similarly, the IHC staining data showed that MPO expression in 2-ClPA and 2-ClHDA treated groups was more than 3-fold higher than in PA and HDA groups, respectively.
In summary, our data indicate that chlorinated lipid, 2-ClPA and 2-ClHDA, elicit inflammatory responses in rat mesentery, which are characterized by elevated leukocyte-endothelial interactions (leukocyte rolling and adhesion), mast cell degranulation, ROS production, and endothelial barrier disruption (albumin leakage). These changes were associated with increased MPO expression level in jejunum submucosa of intestinal segments adjacent to the superfused mesentery in response to the two chlorinated lipid. These inflammatory responses mimic those produced by sepsis, thereby providing evidence supporting the hypothesis that chlorinated lipid, generated from the enzymatic activity of neutrophil-MPO system, induce microcirculatory dysfunction via stimulating inflammatory responses when compared to non-chlorinated lipid. In future studies, we propose to directly test this postulate by applying MPO inhibitors to septic models, and monitoring whether chlorinated lipid production would be reduced and the aforementioned inflammatory responses can be attenuated.