ABSTRACT

4-hydroxy-2-nonenal (4-HNE) is a lipid peroxidation product that is known to be elevated during oxidative stress. During systemic inflammation and endotoxemia, plasma levels of 4-HNE are elevated in response to lipopolysaccharide (LPS) stimulation. 4-HNE is a highly reactive molecule due to its generation of both Schiff bases and Michael adducts with proteins, which may result in modulation of inflammatory signaling pathways. In this study, we report the production of a 4-HNE adduct-specific monoclonal antibody (mAb) and the effectiveness of the intravenous injection of this mAb in ameliorating LPS-induced endotoxemia and liver injury in mice. Endotoxic lethality was suppressed by the administration of anti-4-HNE mAb. After LPS injection, we observed a significant increase in the plasma levels of AST, ALT, IL-6, TNF-α and MCP-1, and elevated expressions of IL-6, IL-10 and TNF-α in the liver. All these elevations were inhibited by anti-4-HNE mAb treatment. As to the underlining mechanism, anti-4-HNE mAb inhibited the elevation of plasma high mobility group box-1 (HMGB1) levels, the translocation and release of HMGB1 in the liver and the formation of 4-HNE adducts themselves, suggesting a functional role of extracellular 4-HNE adducts in hypercytokinemia and liver injury associated with HMGB1 mobilization. In summary, this study reveals a novel therapeutic application of anti-4-HNE mAb for endotoxemia.