

Pneumonia is the major cause of decline in bighorn sheep (BHS) populations in North America. *Mannheimia haemolytica* is an important etiological agent of this disease in BHS. Leukotoxin (Lkt) secreted by *M. haemolytica* is the major virulence factor of this organism. Lkt is a pore-forming exotoxin which is cytotoxic to all subsets of leukocytes. Polymorphonuclear leukocytes (PMNs) are the subset that is most susceptible to Lkt. PMNs of BHS are 4-8 times more susceptible to Lkt-induced cytolysis than those of domestic sheep (DS). In an attempt to elucidate the molecular basis for the enhanced susceptibility of BHS PMNs, we tested two mutually non-exclusive hypotheses in this study: 1. The enhanced susceptibility of BHS PMNs to Lkt-induced cytolysis is due to enhanced binding of Lkt to these cells. We tested this hypothesis by comparing Lkt-binding to PMNs of BHS and DS by flow cytometric analysis. This analysis revealed that Lkt does not bind to BHS PMNs with higher avidity than DS PMNs. 2. The enhanced susceptibility of BHS PMNs to Lkt-induced cytolysis is due to enhanced susceptibility of the plasma membrane of these cells to pore-formation by Lkt. We tested this hypothesis by determining the susceptibility of PMNs of BHS and DS to transmembrane pore-formation. PMNs were incubated with the pore-forming toxins melittin and magainin, and the reduction in viability of the cells due to pore-formation was assessed by the MTT-dye-reduction cytotoxicity assay. This assay indicated that BHS PMNs are not more susceptible to pore-formation by these toxins than DS PMNs. Taken together, these results suggest that the enhanced susceptibility of BHS PMNs to Lkt-induced cytotoxicity is unlikely due to enhanced Lkt-binding, or enhanced susceptibility of their plasma membrane to pore-formation by Lkt.