論 文 要 旨

Early ascorbic acid administration prevents vascular endothelial cell damage in septic mice

（敗血症マウスにおける早期アスコルビン酸投与による血管内皮細胞障害の抑制）

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Oxidation of BH4, a cofactor of nitric oxide synthase (NOS), produces reactive oxygen species (ROS) through uncoupling of NOS and affects vascular endothelial dysfunction. Ascorbic acid (AsA) inhibits the oxidation of BH4 and reduces ROS. However, the kinetic changes of BH4 in sepsis and its effect on the kinetic changes in AsA administration therapy, as well as the appropriate timing of AsA administration for AsA therapy to be effective, are unclear. Mice with sepsis, induced by cecal ligation and puncture (CLP), were examined for the effect of AsA administration (200 mg/kg) on vascular endothelial cell dysfunction at two administration timings: early group (AsA administered immediately after CLP) and late group (AsA administered 12 h after CLP). Survival rates were compared between the early and late administration groups, and vascular endothelial cell damage, indicated by the dihydrobiopterin/tetrahydrobiopterin ratio, serum syndecan-1, and endothelial nitric oxide synthase, as well as liver damage, were examined. The early group showed significantly improved survival compared to the non-treatment group ($p < 0.05$), while the late group showed no improved survival compared to the non-treatment group. Compared to the non-treated group, the early AsA group showed less oxidation of BH4 in sepsis. Syndecan1, a marker of vascular endothelial cell damage, was less elevated and organ damage was reduced in the early AsA-treated group. In septic mice, early AsA administration immediately after CLP may protect vascular endothelial cells by inhibiting BH4 oxidation, thereby reducing organ dysfunction and improving survival.