

論 文 要 旨

Low concentrations of human neutrophil peptide ameliorate experimental murine colitis

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Human neutrophil peptides (HNPs) not only have antimicrobial properties, but also exert multiple immunomodulatory effects depending on the concentration used. We have previously demonstrated that the intraperitoneal administration of high-dose HNP-1 (100 μ g/day) aggravates murine dextran sulfate sodium (DSS)-induced colitis, suggesting a potential pro-inflammatory role for HNPs at high concentrations. However, the role of low physiological concentrations of HNPs in the intestinal tract remains largely unknown. The aim of this study was to examine the effects of low concentrations of HNPs on intestinal inflammation. We first examined the effects of the mild transgenic overexpression of HNP-1 in DSS-induced colitis. HNP-1 transgenic mice have plasma HNP-1 levels similar to the physiological concentrations in human plasma. Compared to wild-type mice treated with DSS, HNP-1 transgenic mice treated with DSS had significantly lower clinical and histological scores, and lower colonic mRNA levels of pro-inflammatory cytokines, including interleukin (IL)-1 β and tumor necrosis factor (TNF)- α . We then injected low-dose HNP-1 (5 μ g/day) or phosphate-buffered saline (PBS) intraperitoneally into C57BL/6N and BALB/c mice administered DSS. The HNP-1-treated mice exhibited significantly milder colitis with reduced expression levels of pro-inflammatory cytokines compared with the PBS-treated mice. Finally, we examined the in vitro effects of HNP-1 on the expression of cytokines associated with macrophage activation. Low physiological concentrations of HNP-1 did not significantly affect the expression levels of IL-1 β , TNF- α , IL-6 or IL-10 in colonic lamina propria mononuclear cells activated with heat-killed *Escherichia coli*, suggesting that the anti-inflammatory effects of HNP-1 on murine colitis may not be exerted by direct action on intestinal macrophages. Collectively, our data demonstrated a biphasic dose-dependent effect of HNP-1 on DSS-induced colitis: an amelioration at low concentrations and an aggravation at high concentrations. Low concentrations of HNPs may contribute to the maintenance of intestinal homeostasis.