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Oligosaccharides from agar inhibit murine intestinal inflammation through the induction of heme oxygenase-1 expression

（アガロオリゴ糖はヘムオキシゲナーゼ-1 の発現誘導を介してマウスの腸管炎症を阻害する）

BACKGROUND:

Agarose is hydrolyzed easily to yield oligosaccharides, designated as agaro-oligosaccharides (AGOs). Recently, it has been demonstrated that AGOs induce heme oxygenase-1 (HO-1) expression in macrophages and that they might lead to anti-inflammatory property. Nevertheless, the molecular mechanism of AGO-mediated HO-1 induction remains unknown, as does AGOs' ability to elicit anti-inflammatory activity *in vivo*. This study was undertaken to uncover the mechanism of AGO-mediated HO-1 induction and to investigate the therapeutic effect of AGOs on intestinal inflammation.

METHODS:

Mice were treated with 2,4,6-trinitrobenzene sulfonic acid (TNBS) to induce colitis. The respective degrees of mucosal injury of mice that had received AGO and control mice were compared. We investigated HO-1 expression using Western blotting, quantitative real-time PCR (qRT-PCR), and immunohistochemistry. The expression of tumor necrosis factor-α (TNF-α) was measured using qRT-PCR and enzyme-linked immunosorbent assay.

RESULTS:

AGO administration induced HO-1 expression in colonic mucosa. The induction was observed mainly in F4/80 positive macrophages. Increased colonic damage and myeloperoxidase activity after TNBS treatment were inhibited by AGO administration. TNBS treatment induced TNF-α expression, and AGO administration suppressed induction. However, HO inhibitor canceled AGO-mediated amelioration of colitis. In RAW264 cells, AGOs enhanced HO-1 expression time-dependently and concentration-dependently and suppressed lipopolysaccharide-induced TNF-α expression. Furthermore, agarotetraose-mediated HO-1 induction required NF-E2-related factor 2 function and phosphorylation of c-jun N-terminal kinase.

CONCLUSIONS:

We infer that AGO administration inhibits TNBS-induced colitis in mice through HO-1 induction in macrophages. Consequently, oral administration of AGOs might be an important therapeutic strategy for inflammatory bowel disease.