

# EFFECT OF COLON INFLAMMATION ON 5-AMINOSALICYLIC ACID METABOLISM

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**BACKGROUND:** The American Gastroenterological Association recommends the need to minimize use of corticosteroids and immunosuppressants for the treatment of Inflammatory Bowel Disease (IBD), a chronic inflammatory condition of the GI tract. Today, drugs based on 5-aminosalicylic acid (5-ASA), are the first-line drug therapy on IBD, particularly in Ulcerative Colitis (UC). 5-ASA acts topically in the colonic mucosa where it is metabolized, by the enzyme arylamine N-acetyltransferase (NAT), to N-acetyl-5-ASA. A large fraction of patients do not respond to this therapy even when disease is mild-to-moderate. Interestingly, the inflammatory factor never has been evaluated on the variable respond to 5-ASA therapy. Using a novel method developed in the laboratory to directly measure 5-ASA metabolism in tissue homogenates, we ask if colonic inflammatory state alters the metabolism of 5-ASA.

**METHODS:** Colon inflammation was induced chemically on C57BL/6J male mice, by administration of 4% dextran sulfate sodium (DSS) in drinking water for 7 days. Mice were sacrificed with overdose of isofluorene and cervical dislocation. Colon was removed, cleaned and opened along the antimesenteric side. Sections of the colon were homogenized on Sorensen's Phosphate Buffer added with protease inhibitors. NAT enzyme was evaluated on its activity and expression, assayed on the colon homogenates. Myeloperoxidase activity was measure as a marker for inflammation.

**RESULTS:** At day 6, mice treated with DSS showed 11% decrease on body weight compared with control group, reaching a 15% on day 7. DSS treatment induced reduction of the length of the colon in more than 50% ( $4.6 \pm 0.5$  cm) compared with control conditions ( $7.0 \pm 0.0$  cm). Visual inspection showed mucosal damage induced by DSS more severe on central and distal sections. Central colon homogenates from mice with DSS colitis showed increase in MPO activity ( $2.3 \pm 1.6$   $\mu\text{mol H}_2\text{O}_2/\text{min}/\text{mg}$ ), compared with control mice ( $0.4 \pm 0.2$   $\mu\text{mol H}_2\text{O}_2/\text{min}/\text{mg}$ ), however, n and variability affected the significance. Interestingly, NAT enzyme showed a significant increase activity ( $7.9 \pm 0.1$  nmol/min/mg) versus control mice ( $5.0 \pm 0.7$  nmol/min/mg). Colitis did not induced changes in NAT protein expression in any section.

**CONCLUSIONS:** This initial study describes, for the first time, a possible relationship between NAT activity and colon inflammation. The study suggests that DSS induces inflammation to varying degrees of severity depending on the area of the colon, with central colon being more susceptible. Central inflammation could be a factor to NAT increases its activity. More studies are needed to confirm those results.