SUMMARY:

Backround and Aim: Glucocorticoids are steroids with antiproliferative and anti-inflammatory effects and are used for treatment of various inflammatory diseases and some tumors. Local concentration of glucocorticoids in tissue is regulated not only by plasma concentration but also enzymatically by 11β-hydroxysteroid dehydrogenase (11βHSD).

11βHSD catalyzes the interconversion of hormonally active C11- hydroxylated corticosteroids (cortisol, corticosterone) and their inactive C11-keto metabolites (cortisone, 11-dehydrocorticosterone). The type 1 and type 2 11βHSD enzymes differ in their physiological roles, regulation and tissue distribution.

Aims: Enhancement of glucocorticoids is able attenuate both inflammation and tumorogenesis. The aim of this study was to investigate the impact of inflammatory bowel disease and colon adenocarcinoma on the activity and expression of colonic 11βHSD1 and 11βHSD2.

Methods: Quantitative real- time RT-PCR was used to assess messenger RNA for 11βHSD1 and 11βHSD2 in bioptic samples taken from patients with ulcerative colitis and healthy controls, and in colon of patients with colon adenocarcinoma and in control surrounding non-neoplastic tissue and in colon of rats with colitis induced by dextran sulfate sodium (DSS) and 2,4,6-trinitrobenzenesulphonic acid (TNBS). Hapten-induced TNBS colitis mimics some of the characteristics of Crohn disease and represents a transmural inflammatory response, second model, DSS colitis, resembles human ulcerative colitis. Metabolism of glucocorticoids in rat colonic tissue was measured in tissue fragments. The activities of 11βHSD1 and 11βHSD2 enzymes in colon adenocarcinoma and control surrounding nonneoplastic tissue were evaluated by a radiometric assay.

Results: In both human and rat speciemens colitis up-regulated the expression of colonic 11βHSD1 mRNA and down-regulated 11βHSD2 mRNA. A similar pattern was observed at the level of local metabolism of glucocorticoids in tissue. Oxidation of corticosterone to 11-dehydrocorticosterone was decreased and reduction of 11-dehydrocorticosterone to corticosterone was increased in colonic tissue of rats with TNBS and DSS-colitis.

Expression and activity 11βHSD2 mRNA were significantly increased in control than in comparsion with neoplastic tissue. Neoplastic transformation was associated in some specimens with an increase of 11βHSD1 mRNA, whereas no change or a weak decrease was observed in other specimens.Activity of 11βHSD1 was undetectable or very low in all control tissues. On the other hand, this activity was clearly increased in some neoplastic tissues.

Conclusions: Colonic inflammation induces local glucocorticoid activation via 11βHSD1 and impairs glucocorticoid inactivation via 11βHSD2. The observed changes indicate a role for local metabolism of glucocorticoids in the control of colonic inflammation.

Our results support the notion that colorectal cancer is associated with a markedly decreased capability of glucocorticoid inactivation via 11βHSD2. In contrast, the expression and activity of 11βHSD1, considered to produce active glucocorticoids from their inactive 11-keto derivatives, was apparently increased in some specimens. Considering that this type of enzyme is expressed predominantly in nonepithelial stroma cells it is tempting to speculate that stroma-derived glucocorticoids might play a role in tumor development.