Abstract

Glucocorticoids play an important role in regulation of inflammation and their immunosuppressive effect is widely used for treatment of inflammatory diseases. The biological activity of glucocorticoids depends not only on their plasma concentrations, the number of receptors and the responsiveness of the target cells but also on the local metabolism of glucocorticoids that is predominated by 11β-hydroxysteroid dehydrogenase (11HSD). Two isoforms of 11HSD are known. The isoform 11HSD1 operates in vivo predominantly as a reductase that increases the local concentrations of glucocorticoids by reduction of their 11-oxo derivatives. The isoform 11HSD2 is a pure dehydrogenase that inactivates biologically active glucocorticoids to their inactive 11-oxo derivatives.

The published data concerning peripheral metabolism of glucocorticoids during inflammation were obtained mostly in in-vitro studies. The aim of the thesis therefore was: (1) to study peripheral metabolism of glucocorticoids during trinitrobenzensulfonic acid (TNBS) induced colitis in rat. (2) to study peripheral metabolism of glucocorticoids in biopsies from human ulcerative colitis (3) to examine peripheral metabolism of glucocorticoids during dextran sodium sulphate (DSS) induced colitis in rat and (4) to study peripheral metabolism of glucocorticoids during adjuvant arthritis in rat. Enzymatic and molecular biology methods were used to study the specific goals.

(1) TNBS induced colitis resulted in significant changes of peripheral metabolism of glucocorticods. 11-reductase activity was strongly up-regulated and 11-oxidase activity down-regulated in inflamed tissue. Concomitantly the expression of 11HSD1 mRNA was up-regulated and 11HSD2 mRNA down-regulated. Treatment with nonselective inhibitor carbenoxolone decreased 11-oxidase activity in the inflamed tissue by almost 50% without any influence on neither expression of proinflammatory cytokines TNF-α, IL1-β nor the infiltration of colon by immune cells.

(2)Ulcerative colitis up-regulated the expression of colonic 11HSD1 mRNA and down-regulated 11HSD2 mRNA. The mRNA expression of pro-inflammatory cytokines was significantly increased in biopsy specimens from patients with ulcerative colitis compared to control biopsies. This effect was probably influenced by proinflammatory cytokines, increased activity of HPA axis and increased infiltration of colon by immune cells.

(3) DSS colitis significantly up-regulated expression of 11HSD1 and down-

regulated expression 11HSD2. In accordance with these changes we found increased 11-reductase activity and decreased 11-oxidase activity compared with control group. These findings fully reflected findings in ulcerative colitis.

(4) Adjuvant arthritis increased synovial 11HSD1 mRNA and 11-reductase activity and in lymph nodes. Administration of carbenoxolone resulted in exacerbation of edema and significantly increased mRNA expression of inflammatory markers TNF-α, COX-2 and OPN, with no change in plasma levels of corticosterone.