Intestinal inflammation modulates expression of 11β-hydroxysteroid dehydrogenase in murine gut

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Abstract

The effect of glucocorticoids is controlled at the pre-receptor level by the activity of 11β-hydroxysteroid dehydrogenase (11HSD). The isoform 11HSD1 is an NADP⁺-dependent oxidoreductase, usually reductase, that amplifies the action of glucocorticoids due to reduction of the biologically inactive 11-oxo derivatives cortisol and 11-dehydrocorticosterone to cortisol and corticosterone. The NAD⁺-dependent isofrm (11HSD2) is an oxidase that restrains the effect of hormones due to 11β-oxidation of cortisol and corticosterone to their 11-oxo derivatives. Although the immunosuppressive and anti-inflammatory effects of glucocorticoids are well known, the relationship between inflammation and local metabolism of glucocorticoids is not well understood. In this study, we demonstrated that colitis induced by dextran sulfate sodium modulates colonic 11HSD1. Experimentally induced intestinal inflammation stimulated colonic NADP⁺-dependent but not NAD⁺-dependent 11HSD activity. Colonic 11HSD1 mRNA was increased, whereas 11HSD2 mRNA was not changed. Additional parallel studies revealed a similar pattern of 11HSD1 mRNA induction in mesenteric lymph nodes and intestinal intraepithelial lymphocytes, but not in spleen and peritoneal macrophages. These data suggest that inflammation modulates local metabolism of glucocorticoid and support the notion that pre-receptor regulation of endogenous corticosteroids might play a role in inflammatory processes.


Introduction

Glucocorticoids are known to be essential modulators of immune and inflammatory processes. They influence the development and effector functions of the immune system, trafficking of immune cells through the vascular bed, and chemotaxis. At the cellular level, they modulate maturation, differentiation, proliferation, and activation of immune cells (Ashwell et al. 2000, Webster et al. 2002). One of the main effects of glucocorticoids is the downregulation of pro-inflammatory cytokines. These cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-1 (IL-1), have been shown to link inflammation with glucocorticoid production by stimulating the hypothalamic–pituitary–adrenal axis and elevating thereby the plasma glucocorticoid concentration (Besedovsky & del Rey 1996). However, the biological activity of glucocorticoids depends not only on their plasma concentration, the number of receptors, and the responsiveness of the target cell, but also on the local metabolism of glucocorticoids catalyzed by 11β-hydroxysteroid dehydrogenase (11HSD), which can change the concentration of active glucocorticoids within tissues and/or target cells.

Two isofoms of 11HSD have been characterized. Isoform 2 (11HSD2) is a high-affinity NAD⁺-dependent enzyme that operates exclusively as an oxidase inactivating biologically active glucocorticoids cortisol and corticosterone to their 11-oxo derivatives cortisone and 11-dehydrocorticosterone respectively (Stewart & Krozowski 1999). In contrast, 11HSD1 is a low-affinity NADP(H)-dependent oxidoreductase whose reductase activity has been found in various intact cells (Seckl & Walker 2001), but alterations in the NADP⁺/NADPH redox potential governed by the metabolism of glucose-6-phosphate via hexose-6-phosphate dehydrogenase seem to determine whether 11HSD1 operates as a reductase or an oxidase (Hewitt et al. 2005). Thus, 11HSD2 decreases the local concentration of active glucocorticoids, whereas 11HSD1 increases it due to regeneration of biologically active steroids from the circulating inactive 11-oxo metabolites or decreases it due to oxidation of active glucocorticoids (Stewart & Krozowski 1999, Seckl & Walker 2001, Hewitt et al. 2005). Exposure to pro-inflammatory stimuli such as TNF-α and IL-1β increases 11HSD1 expression and enzymatic activity in some cells, while inducing a decrease of 11HSD2 in others (Cai et al. 2001, Cooper et al. 2001, Heimiger et al. 2001, Thieringer et al. 2001, Tomlinson et al. 2001). The biological significance of this process was shown recently (Escher et al. 1997, Thieringer et al. 2001, Zhang et al. 2005).

With regard to the colon, 11HSD2 is expressed in epithelial cells, whereas 11HSD1 is localized in the cells of lamina propria (Whorwood et al. 1994). This matches with the findings of 11HSD1 in fibroblasts (Hammani & Siiteri
1991), macrophages (Thieringer et al. 2001), and lymphocytes (Zhang et al. 2005). Consistent with the effect of TNF-α and IL-1β on 11HSD1 and 11HSD2, we have shown in a rat model of colitis that 11HSD1 mRNA expression and 11-reductase activity increased, whereas 11HSD2 mRNA expression and 11-oxidase activity decreased during intestinal inflammation (Bryndová et al. 2004). Considering that colitis is accompanied by activation of mucosal immune cells and increased recruitment of leukocytes from the vascular space (Elson et al. 1995), one can hypothesize that the link between the upregulation of colonic 11HSD1 mRNA and the increased ability of the tissue to reduce 11-dehydrocortico-sterone to corticosterone might be the cells of the intestinal immune system. To address this question, we used the dextran sulfate model of murine colitis and studied the changes of 11HSD1 in colon and immune cells during intestinal inflammation.

Materials and Methods

Animals and preparation of immune cells

Female 3-month-old mice Balb/c (Velaz, Prague, Czech Republic) were used in this study. Experimental colitis was induced by adding 3% (w/v) dextran sulfate sodium (DSS, MW 36 000–50 000; ICN Biomedicals Inc., Cleveland, Ohio, USA) in drinking water (Okayasu et al. 1990). Mice were treated with DSS for 7 days and subsequently killed. Control animals received only tap water. The mice were killed by decapitation and the colon, spleen, and mesenteric lymph nodes were excised. Macrophages were collected by a thiocyanate method. The isolated RNA was treated with Mammalian Total RNA Miniprep Kit (Sigma). cDNA was synthesized from 5 μg RNA and M-MLV Reverse Transcriptase reagents (Invitrogen GmbH). Amplification of the target cDNA was performed in the LightCycler (Roche) as previously reported (Mazancová et al. 2005) using QuantiTect Sybr Green PCR Kit (Qiagen GmbH) and the primers given in Table 1. Results were analyzed with LightCycler software using the second derivative maximum method to set Cq. For the quantification of the target genes 11HSD1, 11HSD2, TNF-α, and IL-1β, we performed the quantitative comparison of several candidate reference genes to select the most stable genes for gene normalization. The panel of five reference genes generally used in many physiological and pathophysiological conditions, such as β-actin (ACTB), hypoxanthine phosphoribosyltransferase 1 (HPRT1),

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sense (5’→3’)</th>
<th>Antisense (5’→3’)</th>
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<tbody>
<tr>
<td>11HSD1</td>
<td>GGTAGTGTCCTCGCTGCTTGAA</td>
<td>CACGTTGACCTTGTTAGTACTAGAGTT</td>
</tr>
<tr>
<td>11HSD2</td>
<td>CCGGTGTGACATGGTCTTTTG</td>
<td>GGGGTATGGCATGTCTGGGGT</td>
</tr>
<tr>
<td>TNF-α</td>
<td>GGACAAGGTGCTCCCCGGACTAC</td>
<td>TCTGAGCCATAATCCTCTTTTC</td>
</tr>
<tr>
<td>IL-1β</td>
<td>TCCCAAGCAATACCCAAAGAAGAA</td>
<td>ATCCAGGGCAAGGGGAGGAAACACAG</td>
</tr>
<tr>
<td>β-actin</td>
<td>GAACCCCTAAGGCCAACCCGTTGAA</td>
<td>ACCGCTCTTGACCAAAGATGCTAG</td>
</tr>
<tr>
<td>Ppib</td>
<td>AGGGAGATGCGCACAAGGAAAAAGGC</td>
<td>ACGCGCATCAGCAGCCACGAG</td>
</tr>
<tr>
<td>EF1α</td>
<td>TGACAGCAAAGAGGCCACCCCAAT</td>
<td>GGCATCCTCCAGCTTCAACA</td>
</tr>
<tr>
<td>RPL13A</td>
<td>CTCCCCAGGCCCTATCACATT</td>
<td>GGCCCTTTCCTCTCCCTTCTCTCCTCT</td>
</tr>
<tr>
<td>HPRT</td>
<td>GCAGTCCAGCAGGTCTG</td>
<td>TATGTAATCAGCAGGCAGCG</td>
</tr>
</tbody>
</table>

The animal study was approved by the Animal Care and Use Review Committee of the Czech Academy of Sciences.

Evaluation of colitis

The clinical assessment of DSS-treated animals included body weight, colon length, evaluation of stool consistency, and the presence of blood in the stool. A clinical disease activity index representing the sum of separate scores ranging from 0 to 4 was calculated using the following parameters: body weight decrease (0, less than 5% decrease; 1, 5–10%; 2, 10–20%; 4, more than 20%), stool consistency (solid 0, loose 2, diarrhea 3), and bleeding (none 0, macroscopic in colon 2, blood adhering to the anus 4) as described previously (Bendjelloul et al. 2000).

Quantitative analysis of 11HSD and cytokine RNA

Total RNA from the colon was extracted by the guanidinium thiocyanate method. The isolated RNA was treated with DNase (Promega) to remove potential contamination by genomic DNA as mentioned earlier (Mazancová et al. 2003). Total RNA from the spleen, mesenteric lymph nodes, macrophages, and IEL was obtained using GeneElute Mammalian Total RNA Miniprep Kit (Sigma). cDNA was synthesized from 5 μg RNA and M-MLV Reverse Transcriptase reagents (Invitrogen GmbH). Amplification of the target cDNA was performed in the LightCycler (Roche) as previously reported (Mazancová et al. 2005) using QuantiTect Sybr Green PCR Kit (Qiagen GmbH) and the primers given in Table 1. Results were analyzed with LightCycler software using the second derivative maximum method to set Cq. For the quantification of the target genes 11HSD1, 11HSD2, TNF-α, and IL-1β, we performed the quantitative comparison of several candidate reference genes to select the most stable genes for gene normalization. The panel of five reference genes generally used in many physiological and pathophysiological conditions, such as β-actin (ACTB), hypoxanthine phosphoribosyltransferase 1 (HPRT1),
ribosomal protein L13a (RPL13A), elongation factor 1α (EF1A), and peptidylprolyl isomerase B (cyclophilin B; PPIB), were tested (Table 1). Because of the high concentration of β-actin and 11HSD2, the samples were diluted 1/1000 before analyses of these RNA species. For other analyses, 1/10 pre-diluted cDNA was used as a template for PCR. Calibration curves were generated for each pair of primers from serial dilutions of standard cDNA. After statistical analysis of reference genes, the data of target gene expression were normalized according to the normalization factor calculated by the geNorm applet (Vandesompele et al. 2002).

The expression of 11HSD1 mRNA in IEL was determined by the ABI PRISM 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The probes and primers used for this experiment were developed as TaqMan Gene Expression Assays by Applied Biosystems. The reaction was carried out in a final volume of 20 μl using TaqMan Universal PCR Master Mix with AmpEraseUNG (Applied Biosystems) and Expression Assay. Target 11HSD1 mRNA was achieved using calibration curve method and the amount of mRNA was normalized to the level of 18S rRNA (Bas et al. 2004).

Enzyme activity assays
Colon homogenates were prepared in ice-cold buffers containing 10 mM Tris, 250 mM sucrose (pH 8.5; 11HSD2 assay) or 10 mM Tris, 5 mM EDTA, 0.5% Triton X-100 (pH 7.5; 11HSD1 assay). After centrifugation at 500 g for 15 min, the supernatant was obtained and protein concentration was measured using the Bradford technique (Bradford, 1976). 11HSD1 and 11HSD2 activities were measured as NADP+ and NAD+ dependent 11β-oxidation of corticosterone according to Livingstone & Walker (2003) and Gomez-Sánchez et al. (2003). 11HSD1 activity was measured in incubation buffer containing 50 mM Tris, 100 mM KCl, 1 mM NADP+, 480 nM corticosterone, and 20 nM 1,2,6,7-[3H]corticosterone (pH 7.5). 11HSD2 activity was determined in a similar way, with 50 mM Tris, 100 mM KCl, 1 mM NAD+, and 20 nM 1,2,6,7-[3H]corticosterone (pH 8.5). The amounts of protein and the incubation times were determined in preliminary experiments to establish the optimal conditions, in order to work in the linear portion of the enzyme reaction. Steroids were extracted from the incubation buffer by SepPak cartridges (Waters, Milford, MA, USA) and separated by HPLC with on-line detection using a flow-cell detector (Radiomatic 150/TR, Canberra Packard, Meriden, CT, USA). The separation was performed in a C18 column using a water methanol gradient (for details see Pácha et al. 2004).

Data analysis
All data are expressed as means ± S.E.M. or medians with 25th–75th percentile values. The distribution–fitting procedure according to Shapiro–Wilk’s W-test of normality was applied and the comparison between the control animals and the mice with colitis was analyzed using unpaired Student’s t-test or Mann–Whitney U-test. The values P<0.05 were considered statistically significant. For stability comparison of candidate reference genes and the calculation of normalization factor, the geNorm program was applied after conversion of Cp values into relative quantities (Vandesompele et al. 2002). Using this approach, the normalization factor based on two candidate reference genes was calculated. Statistical analysis was performed using the statistical software Statistica v.6 (StatSoft Inc., Tulsa, OK, USA).

Results
The mice with colitis developed loose stools or diarrhea associated with blood in the stool and decreased colon length and body weight. Mortality was 10%. The index of disease activity is given in Table 2.

To investigate whether metabolism of glucocorticoids is modulated in inflamed tissue, we used enzyme assay and quantitative reverse transcription (RT)-PCR. First, we evaluated the expression levels of five putative reference genes in the colon of healthy mice and in animals with colitis. These genes displayed a relatively wide range of CP (Fig. 1). Using the unpaired Student’s t-test or Mann–Whitney U-test, significant differences in gene expression between healthy and inflamed colon were observed for EF1A and RPL13A. The geNorm program was then used to calculate the gene expression stability measure M of the remaining genes and the normalization factor based on the geometric average of the two reference genes (Vandesompele et al. 2002). We found ACTB and PPIB to be the most convenient reference genes and thus these two genes were used for normalization of mRNA expression levels.

To determine whether 11HSDs are modulated during inflammation, we measured colonic 11HSD1 and 11HSD2 mRNAs in control animals and in mice with colitis. As shown in Fig. 2, both groups of mice were found to express 11HSD1 and 11HSD2 transcripts and the inflammation affected the expression. Colitis upregulated 11HSD1 mRNA but did not

Table 2 Disease activity of DSS-induced colitis in colon

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Acute colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>0-0 (0-0-0-0)</td>
<td>8-0 (6-0-10-0)*</td>
</tr>
<tr>
<td>Diarrhea score</td>
<td>0-0 (0-0-0-0)</td>
<td>3-0 (3-0-3-0)*</td>
</tr>
<tr>
<td>Blood score</td>
<td>0-0 (0-0-0-0)</td>
<td>4-0 (0-0-4-0)</td>
</tr>
<tr>
<td>Body weight change</td>
<td>2-0±0.8</td>
<td>−11-4±1.5*</td>
</tr>
<tr>
<td>Colon length</td>
<td>9-9±0.3</td>
<td>7-3±0.1*</td>
</tr>
</tbody>
</table>

The data are given as medians and 25th–75th percentile values (score values) or mean ± S.E.M. (body weight change, colon length) based on records of 10 control and 9 DSS-treated animals. The score values were calculated as mentioned in Materials and Methods section. Colon length is given in cm, and body weight change is given by dividing body weight at day 7 by body weight at day 0 (starting body weight) and is expressed as a percentage. *P<0.05 compared with controls.
significantly modulate the levels of 11HSD2 mRNA. To test whether the changes in transcript levels reflect changes in 11HSD1 and 11HSD2 enzyme activities, we used a colonic homogenate assay to analyze the NAD\(^+\) and NADP\(^+\)-dependent conversion of corticosterone to 11-dehydrocorticosterone. The colon of controls and the mice with colitis had similar level of NAD\(^+\)-dependent 11HSD activity, but NADP\(^+\)-dependent 11HSD activity was significantly increased in inflamed tissue (Fig. 3). To verify the presence of colonic inflammation in this tissue, we analyzed gene expression of pro-inflammatory cytokines, TNF-\(\alpha\) and IL-1\(\beta\) mRNAs. As shown in Table 3, the level of IL-1\(\beta\) transcript was significantly increased in inflamed colon but the level of TNF-\(\alpha\) transcript was changed much less, in a similar way as in the study of Egger et al. (2000) and Kwon et al. (2005).

Next, we evaluated the changes in the level of 11HSD1 mRNA in the cells of gut-associated lymphatic tissue. There was a significant increase in 11HSD1 mRNA in IEL isolated

### Table 3 Expression of TNF-\(\alpha\) and IL-1\(\beta\) mRNAs in colon

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Acute colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-(\alpha) mRNA</td>
<td>(0.202 \pm 0.063)</td>
<td>(0.258 \pm 0.61)</td>
</tr>
<tr>
<td>IL-1(\beta) mRNA</td>
<td>(0.023 \pm 0.002)</td>
<td>(0.356 \pm 0.183^*)</td>
</tr>
</tbody>
</table>

The data are given as means \(\pm\) S.E.M. of 10 control and 9 DSS-treated animals. The expression of cytokines is given in arbitrary units. \(^*\)P<0.05 compared with controls.
from animals with colitis (Fig. 4). Consistent with upregulation of 11HSD1 mRNA in IEL, the lymphatic mesenteric nodes that contain large numbers of lymphocytes coming from the intestine demonstrated upregulation of 11HSD1 mRNA (Fig. 5), whereas 11HSD2 transcript was undetectable in the same nodes. In contrast to mesenteric lymph nodes, 11HSD1 transcript in spleen was not changed during colitis. Finally, to establish the potential contribution of macrophages to upregulation of colonic 11HSD1 during inflammation, the peritoneal macrophage 11HSD1 transcript was quantified. 11HSD1 mRNA was detectable in macrophages, but this transcript was not affected by colitis (controls: 0.56 ± 0.05 (n = 10); colitis: 0.48 ± 0.04 (9)). Taken together, these findings demonstrate similar changes in 11HSD1 mRNA in the colon, mesenteric lymphatic nodes, and IEL, but not in the spleen and peritoneal macrophages.

Discussion

The present study revealed that inflammation is associated with changes in 11HSD1 mRNA expression and enzyme activity in colon. The inflamed colon upregulated 11HSD1 transcript and NADP⁺-dependent 11HSD activity without any significant changes in 11HSD2 transcript and NAD⁺-dependent 11HSD activity. As 11HSD2 is expressed only in epithelium, whereas 11HSD1 is expressed in the submucosal layer (Whorwood et al. 1994), it is likely that changes in 11HSD1 proceed in the intestinal compartment of lamina propria or gut-associated lymphatic tissue and not in the epithelium. 11HSD1 was found in macrophages (Thieringer et al. 2001), T cells (Zhang et al. 2005), and fibroblasts (Hamnami & Siiteri 1991), and we have found an increased level of 11HSD1 mRNA in IEL and mesenteric lymphatic nodes of mice with colitis. The question is what is the direction of 11HSD1 reaction in intact cells in vivo? This direction (11β-reduction or 11β-oxidation) depends on the ratio of NADPH/NADP⁺, which is determined by hexose-6-phosphate dehydrogenase and pentose-phosphate pathway (Atanasov et al. 2004, McCormick et al. 2006). Thus, it is difficult to anticipate the reaction direction of 11HSD1 in inflamed colon. Considering that 11HSD1 operates as a reductase in activated macrophages (Gilmour et al. 2006), lymphocytes (Zhang et al. 2005), and dendritic cells (Freeman et al. 2005), it is likely that colonic 11HSD1 is increased by a shift in favor of the reductase activity. Further studies are needed to clarify the role of 11HSD isoforms of colonic wall in vivo by cellular distribution of 11HSDs in cell types of colonic mucosa and submucosa during inflammation and the effect of NADPH depletion during oxidative stress on the direction of the reaction catalyzed by 11HSD1 in immune cells.

The exact mechanism of inflammation induced by DSS is not yet fully elucidated, but the pathogenesis seems to depend on the interaction between local immune reaction and environmental factors because animal models of inflammatory bowel disease reared in germfree conditions did not develop the disease (Tlaskalová-Hogenová 1997, Hudcovic et al. 2001, Elson & Cong 2002). Drinking of DSS generates in murine colon the upregulation of pro-inflammatory cytokines as well as reactive oxygen and nitrogen species and infiltration by polymorphonuclear and mononuclear cells (Okayasu et al. 1990, Kojuharoff et al. 1997, Arai et al. 1998). Previous data and our findings suggest that these processes are accompanied by upregulation of 11HSD1 in the cells of gut-associated lymphatic tissue. First, activated macrophages and lymphocytes acquire increased capacity of glucocorticoid reactivation via 11HSD1 (Zhang et al. 2005). Secondly, our data show that NADP⁺-dependent but not NAD⁺-dependent activity is increased in inflamed colon. Thirdly, the level of 11HSD1 transcript is increased not only in inflamed colon but also in IEL and in mesenteric lymphatic nodes. This upregulation of 11HSD1 is presumably induced by the pro-inflammatory cytokines, whose levels of transcript and protein are increased in colon of DSS-treated mice (Arai et al. 1998, Egger et al. 2000, Obermeier et al. 2002, Kwon et al. 2005). The cytokines TNF-α and IL-1β are known to increase 11HSD1 mRNA and 11-reductase activity in various cell types, such as glomerular mesangial cells (Escher et al. 2005).
Hennebold inducible cytokines in lymphocytes and macrophages bacterial diseases and these changes in resistance following greatly enhanced the susceptibility to progressive in vivo 1997). Similarly, the pharmacological inhibition of 11HSD that the bioavailability of glucocorticoids in inflamed colon notion that inflammation is associated with changes in expression of this enzyme may serve to enhance the exposure in glucocorticoid action, we can speculate that the increased phospholipase A2, a key enzyme producing inflammatory processes (Elenkov & Chrousos 1999, McKay & Cidlowski 1999). Using glomerular mesangial cells exposed to IL-1 and TNF-α, it was demonstrated that the release of phospholipase A2, a key enzyme producing inflammatory mediators, is decreased by 11HSD1 activity (Escher et al. 1997). Similarly, the pharmacological inhibition of 11HSD in vivo greatly enhanced the susceptibility to progressive bacterial diseases and these changes in resistance following 11HSD inhibition correlated with changes in the patterns of inducible cytokines in lymphocytes and macrophages (Hennebold et al. 1997). Given the central role of 11HSD1 in glucocorticoid action, we can speculate that the increased expression of this enzyme may serve to enhance the exposure of immune cells to active glucocorticoids via the paracrine and/or intracrine pathway.

In summary, our observations are consistent with the notion that inflammation is associated with changes in 11HSD1. Although the mechanism and accurate function of 11HSD1 upregulation is equivocal, the findings suggest that the bioavailability of glucocorticoids in inflamed colon differs from the healthy tissue.

Acknowledgements

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