Patients With IgA Nephropathy Have Altered Levels of Immunomodulatory C19 Steroids. Glucocorticoid Therapy With Addition of Adrenal Androgens May Be the Choice

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Summary
Glucocorticoid (GC) therapy is one of the methods of choices for treatment of autoimmune diseases (ADs). In addition, adrenal androgens are known as immunoprotective GC-antagonists. Adrenal steroids preferentially influence the Th1-components over the Th2 ones. We investigated steroid metabolome (using gas chromatography-mass spectrometry) in healthy controls (H), GC-untreated patients with ADs different from IgA nephropathy (U), GC-treated patients with ADs different from IgA nephropathy (T) and in patients with IgA nephropathy (IgAN), which were monitored on the beginning (N0), after one week (N1) and after one month (N2) of prednisolone therapy (60 mg of prednisolone/day/m² of body surface). Between-group differences were assessed by one-way ANOVA, while the changes during the therapy were evaluated by repeated measures ANOVA. The ANOVA testing was followed by Duncan’s multiple comparisons. IgAN patients and patients with other ADs exhibited lack of adrenal androgens due to attenuated activity of adrenal zona reticularis (ZR). Androgen levels including their 7α-, 7β-, and 16α-hydroxy-metabolites were further restrained by GC-therapy. Based on these results and data from the literature, we addressed the question, whether a combination of GCs with Δ⁵-steroids or their more stable synthetic derivatives may be optimal for the treatment of antibodies-mediated ADs.

Key words
Glucocorticoid therapy • Adrenal androgens • Immunomodulatory steroids • Gas chromatography-mass spectrometry • Steroid metabolome

Introduction
IgA nephropathy (IgAN) is the most frequent primary glomerulonephritis worldwide. In this autoimmune disease, aberrantly O-glycosylated IgA1 hinge region serves as an antigen recognized by anti-glycan antibodies. This stimulates a formation of nephritogenic immune complexes (Mestecky et al. 2013), the accumulation of which in the kidney mesangium induces a proliferation of mesangial cells, expansion of extracellular matrix proteins and renal injury, leading to an end-stage renal failure in 20-40 % of patients. Progressive IgAN patients may be treated with glucocorticoids (GCs) (Lai et al. 2016, Matousovic et al. 2015). However, this therapy in IgAN is questionable (Lv et al. 2012, Rauen et al. 2015, Tesar et al. 2015). Although GC-administration represents the most powerful therapy for rapid attenuation of inflammatory response, longtime GC-treatment is accompanied by serious complications such as disruption of hypothalamo-pituitary-adrenal (HPA) axis and inhibition of gonadal activity (Mastorakos et al. 2006, Rengarajan and Balasubramanian 2008). As adrenal androgens are GC-antagonists, we evaluated their levels in groups of healthy controls (H), GC-untreated (U) and GC-treated
(T) patients with other autoimmune diseases (ADs), and in IgAN patients before prednisolone treatment (N0), and after one week (N1) and one month (N2) of prednisolone therapy. Since natural 7α/β- and 16α-hydroxy-steroids are immunomodulatory, anti-inflammatory and immunoprotective (Ahlem et al. 2011a, Ahlem et al. 2011b, Auci et al. 2009, Conrad et al. 2010, Hennebert et al. 2007, Le Mee et al. 2008, Loria 2002, Pettersson et al. 2010, Reading et al. 2012, Tang et al. 2006) we focused on these substances.

Methods

Subjects

The study enrolled 23 women and 43 men. The study groups consisted of healthy controls (H, n=10), untreated controls without IgAN but suffering from other ADs (U, n=10), GC treated non-IgAN controls suffering from other ADs (T, n=9), and patients with IgAN (n=14) who were monitored before prednisolone treatment (N0), after one week (N1) and one month (N2) of prednisolone therapy. The U-group enrolled patients with idiopathic membranous glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, glomerulopathy, and suspensia chronic mesangioproliferative glomerulonephritis. The T-group consisted of patients with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic impairment of connective tissues, polymyalgia rheumatica and giant cell arteritis, membranous nephropathy, complete nephrotic syndrome and glomerulor and segmental glomerulosclerosis. Prednisolone dose was 60 mg of prednisolone/day/m² of body surface. The patients have been recruited from the Nephrological Outpatient Department (NOPD) of the Motol University Hospital and from the neighboring NOPDs in Prague and NOPD of Palacký University Olomouc. No samples from the female subjects were collected in the luteal menstrual phase. The mean age of the participants was 48.4 ± 15.1 years (mean ± SD) and the age differences between the study groups were insignificant.

The Ethics Committee of the Institute of Endocrinology in Prague approved the protocol of the study, and written informed consent was obtained from all participants.

Analytical methods

The circulating levels of steroids and their polar conjugates were measured using a previously described gas chromatographic-mass spectrometric method (Hill et al. 2010).

Statistical analysis

The between-group differences were evaluated using one-way ANOVA. Changes in steroid levels were assessed using repeated measures ANOVA. The ANOVA testing was followed by Duncan’s multiple comparisons (Duncan 1955). The original data were transformed by power transformations to attain Gaussian data distribution and constant variance. Statgraphics Centurion, version XV statistical software from Manugistics, (Herndon, MA, USA) was used for the calculations.

Results

Steroid levels

Most steroids showed significant between-group differences (Table 1) and there was a trend of decreasing in steroid levels during the prednisolone therapy (Table 2). Estradiol was higher in the IgAN patients irrespectively of GC-treatment.

Shifted balance between adrenal C21 and C19-Δ⁴-steroids towards the C21 steroids in IgAN patients

Dehydroepiandrosterone (DHEA) to pregnenolone ratio (Fig. 1A) was higher in the H-group than in the other groups while the dehydroepiandrosterone sulfate (DHEAS) to pregnenolone sulfate ratio did not significantly differ between the H and N0-groups (Fig. 1B). Both ratios (reflecting CYP17A1 – lyase step) decreased during the GC-treatment of IgAN patients. The values and statistics for repeated measures ANOVA in the DHEA/pregnenolone ratio were F=26.51, p<0.001: N0=5.66 (4.72, 6.73 – mean with 95% confidence limits), N1=2.7 (2.14, 3.36), N2=2.06 (1.57, 2.64), N0-N1, N0-N2 (significant differences between stages N0 and N1 and between stages N0 and N2). For the DHEAS/pregnenolone sulfate ratio they were F=4.02, p=0.031: N0=15.2 (12.3, 18.6), N1=11.9 (9.69, 14.5), N2=10.1 (8.22, 12.4), N0-N2.

Increased conversion of DHEA to androstenedione reflecting type 2 3β-hydroxysteroid dehydrogenase (HSD3B2) activity in IgAN patients

Androstenedione/DHEA (Fig. 1C) and androstenedione/DHEAS (Fig. 1D) ratios reflecting type 2 3β-hydroxysteroid dehydrogenase (HSD3B2) activity were higher in the GC-treated groups. The values
Fig. 1. Product to precursor ratios (PPRs) in groups of healthy controls (H), glucocorticoid-untreated patients with autoimmune diseases (ADs) different from IgA nephropathy (IgAN) (U), GC-treated patients with non-IgAN ADs (T) and in IgAN patients on the beginning of prednisolone treatment (N0), after one week (N1) and after one month (N2) of the therapy. The circles with error bars represent re-transformed means with their 95% confidence intervals (for details see section Statistical analysis). The embedded tables show all significant between-group differences (p<0.05) as evaluated by Duncan’s multiple comparisons. The symbols separated by hyphen represent significant between-group differences (p<0.05). Panels A and B show the PPRs reflecting a balance between adrenal C21 and C19-Δ5-steroids, while panels C and D show the PPRs reflecting the activity of type 2 17β-hydroxysteroid dehydrogenase (HSD17B2).
Table 1. Levels of Δ5-steroids, their metabolites and estradiol in healthy controls (H), corticoid-untreated (U) and corticoid-treated patients with autoimmune diseases different from IgA nephropathy (T) and patients with IgA nephropathy on the beginning of prednisolone therapy (N0), on one week (N1) and one month (N2) of prednisolone therapy.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>H</th>
<th>U</th>
<th>T</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (lower 95% confidence limit, upper 95% confidence limit)</td>
<td>F=0.64, p=0.670</td>
<td>F=5.32, p&lt;0.001, H-T, H-N1, H-N2, U-T, U-N1, U-N2, T-N0, N0-N1, N0-N2</td>
<td>F=6.84, p&lt;0.001, H-T, H-N1, H-N2, N0-N1, N0-N2</td>
<td>F=9.35, p&lt;0.001, H-T, H-N1, H-N2, U-T, U-N1, U-N2, T-N0, N0-N1, N0-N2</td>
<td>F=3.92, p=0.004, H-T, U-N0, T-N1, T-N1, T-N2</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>0.884 (0.568, 1.47)</td>
<td>0.91 (0.582, 1.52)</td>
<td>0.666 (0.423, 1.13)</td>
<td>1.07 (0.72, 1.69)</td>
<td>0.846 (0.583, 1.29)</td>
<td>0.71 (0.498, 1.06)</td>
</tr>
<tr>
<td>Pregnenolone sulfate</td>
<td>82.8 (51.6, 132)</td>
<td>72 (44.7, 115)</td>
<td>29.9 (17.2, 51.3)</td>
<td>87.2 (58.6, 129)</td>
<td>35.8 (23.7, 53.7)</td>
<td>30.8 (20.3, 46.3)</td>
</tr>
<tr>
<td>20α-Dihydroprogrenolone</td>
<td>2.64 (1.85, 3.8)</td>
<td>1.53 (1.08, 2.19)</td>
<td>1.28 (0.871, 1.91)</td>
<td>1.86 (1.38, 2.52)</td>
<td>1.1 (0.819, 1.48)</td>
<td>0.962 (0.719, 1.29)</td>
</tr>
<tr>
<td>20α-Dihydroprogrenolone sulfate</td>
<td>421 (240, 688)</td>
<td>348 (193, 582)</td>
<td>144 (61.2, 291)</td>
<td>336 (204, 524)</td>
<td>117 (60, 207)</td>
<td>113 (57.5, 201)</td>
</tr>
<tr>
<td>16α-Hydroxyprogrenolone</td>
<td>0.256 (0.129, 0.508)</td>
<td>0.172 (0.0867, 0.34)</td>
<td>0.077 (0.036, 0.164)</td>
<td>0.56 (0.314, 1)</td>
<td>0.325 (0.182, 0.581)</td>
<td>0.218 (0.123, 0.39)</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>11.9 (6.88, 20.3)</td>
<td>4.42 (2.5, 7.7)</td>
<td>2.38 (1.24, 4.49)</td>
<td>6.43 (4.01, 10.2)</td>
<td>2.35 (1.44, 3.81)</td>
<td>1.75 (1.07, 2.85)</td>
</tr>
<tr>
<td>DHEA sulfate</td>
<td>2310 (1270, 3990)</td>
<td>749 (365, 1430)</td>
<td>276 (106, 635)</td>
<td>1520 (886, 2490)</td>
<td>429 (222, 780)</td>
<td>327 (164, 610)</td>
</tr>
<tr>
<td>7α-Hydroxy-DHEA</td>
<td>0.643 (0.37, 1.09)</td>
<td>0.349 (0.195, 0.608)</td>
<td>0.161 (0.08, 0.313)</td>
<td>0.566 (0.354, 0.889)</td>
<td>0.234 (0.138, 0.387)</td>
<td>0.285 (0.173, 0.461)</td>
</tr>
<tr>
<td>7β-Hydroxy-DHEA</td>
<td>0.36 (0.217, 0.612)</td>
<td>0.208 (0.128, 0.346)</td>
<td>0.116 (0.0665, 0.207)</td>
<td>0.403 (0.261, 0.632)</td>
<td>0.278 (0.179, 0.438)</td>
<td>0.228 (0.15, 0.351)</td>
</tr>
<tr>
<td>Androstenediol</td>
<td>1.57 (0.868, 2.66)</td>
<td>0.865 (0.433, 1.57)</td>
<td>0.577 (0.228, 1.24)</td>
<td>1.21 (0.714, 1.95)</td>
<td>0.712 (0.389, 1.21)</td>
<td>0.61 (0.326, 1.06)</td>
</tr>
<tr>
<td>Androstenediol sulfate</td>
<td>612 (271, 1230)</td>
<td>190 (70.3, 435)</td>
<td>120 (34.3, 324)</td>
<td>528 (272, 948)</td>
<td>332 (160, 630)</td>
<td>193 (84.7, 391)</td>
</tr>
<tr>
<td>5-Androsten-3β,7α,17β-triol</td>
<td>0.065 (0.030, 0.153)</td>
<td>0.032 (0.016, 0.069)</td>
<td>0.025 (0.012, 0.056)</td>
<td>0.177 (0.084, 0.415)</td>
<td>0.084 (0.043, 0.177)</td>
<td>0.068 (0.036, 0.142)</td>
</tr>
<tr>
<td>5-Androsten-3β,7β,17β-triol</td>
<td>0.058 (0.026, 0.143)</td>
<td>0.023 (0.012, 0.050)</td>
<td>0.016 (0.008, 0.037)</td>
<td>0.124 (0.058, 0.299)</td>
<td>0.053 (0.027, 0.112)</td>
<td>0.037 (0.020, 0.075)</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>3.79 (2.47, 5.77)</td>
<td>2.74 (1.77, 4.2)</td>
<td>2.57 (1.57, 4.16)</td>
<td>3.54 (2.46, 5.05)</td>
<td>2.29 (1.58, 3.3)</td>
<td>1.86 (1.28, 2.7)</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.046 (0.021, 0.10)</td>
<td>0.027 (0.013, 0.059)</td>
<td>0.030 (0.013, 0.071)</td>
<td>0.143 (0.064, 0.333)</td>
<td>0.108 (0.048, 0.248)</td>
<td>0.106 (0.048, 0.244)</td>
</tr>
</tbody>
</table>

The differences were evaluated by one-way ANOVA after Box-Cox transformations of original data for attainment of Gaussian distribution and constant variance. The ANOVA testing was followed by Duncan’s multiple comparisons. F and p represent F-statistics and their p-values, respectively. The steroid levels are shown as retransformed means with their 95% confidence intervals. F represents Fisher's statistics in ANOVA testing and p symbolizes its significance level. The symbols separated by hyphen represent significant between-group differences (p<0.05).
Table 2. Levels of Δ5-steroids and their metabolites in patients with IgA nephropathy on the beginning of prednisolone therapy (N0), on one week (N1), and one month (N2) of prednisolone therapy.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Mean (lower 95% confidence limit, upper 95% confidence limit)</th>
<th>Factor Stage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0</td>
<td>N1</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>1.05 (0.81, 1.39)</td>
<td>0.833 (0.658, 1.08)</td>
</tr>
<tr>
<td>Pregnenolone sulfate</td>
<td>87.2 (68.3, 111)</td>
<td>35.8 (27.8, 46)</td>
</tr>
<tr>
<td>20α-Dihydropregnenolone</td>
<td>1.83 (1.47, 2.29)</td>
<td>1.07 (0.877, 1.32)</td>
</tr>
<tr>
<td>20α-Dihydropregnenolone sulfate</td>
<td>299 (231, 388)</td>
<td>107 (82.8, 139)</td>
</tr>
<tr>
<td>16α-Hydroxypregnenolone</td>
<td>0.552 (0.409, 0.748)</td>
<td>0.321 (0.239, 0.434)</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>6.48 (5.07, 8.25)</td>
<td>2.37 (1.82, 3.08)</td>
</tr>
<tr>
<td>DHEA sulfate</td>
<td>1280 (937, 1790)</td>
<td>396 (313, 510)</td>
</tr>
<tr>
<td>7α-Hydroxy-DHEA</td>
<td>0.555 (0.364, 0.849)</td>
<td>0.28 (0.184, 0.426)</td>
</tr>
<tr>
<td>7β-Hydroxy-DHEA</td>
<td>0.414 (0.306, 0.556)</td>
<td>0.279 (0.198, 0.392)</td>
</tr>
<tr>
<td>Androstenediol</td>
<td>1.46 (1.2, 1.74)</td>
<td>0.779 (0.603, 0.978)</td>
</tr>
<tr>
<td>Androstenediol sulfate</td>
<td>435 (352, 539)</td>
<td>280 (227, 346)</td>
</tr>
<tr>
<td>5-Androsten-3β,7α,17β-triol</td>
<td>0.182 (0.128, 0.265)</td>
<td>0.086 (0.062, 0.121)</td>
</tr>
<tr>
<td>5-Androsten-3β,7β,17β-triol</td>
<td>0.145 (0.098, 0.216)</td>
<td>0.060 (0.041, 0.088)</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>3.72 (3.02, 4.51)</td>
<td>2.83 (2.19, 3.55)</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.187 (0.131, 0.244)</td>
<td>0.203 (0.15, 0.255)</td>
</tr>
</tbody>
</table>

*The changes in steroid levels were evaluated by repeated measures ANOVA consisting of factors Stage and Subject after Box-Cox transformations of original data for attainment of Gaussian distribution and constant variance. For explanation of remaining symbols, see Table 1. The ANOVA testing was followed by Duncan's multiple comparisons. F and p represent F-statistics and their p-values, respectively. The steroid levels are shown as retransformed means with their 95% confidence intervals. F represents Fisher's statistics in ANOVA testing and p symbolizes its significance level. The symbols separated by hyphen represent significant between-group differences (p<0.05).
and statistics for repeated measures ANOVA for the androstenedione/DHEA ratio were F=7.23, p=0.003: N0=0.561 (0.422, 0.738), N1=0.983 (0.755, 1.27), N2=1.07 (0.824, 1.38), N0-N1, N0-N2. For the androstenedione/DHEAS ratio they were F=17.61, p<0.001: N0=0.0028 (0.0021, 0.0037), N1=0.0066 (0.0052, 0.0081), N2=0.0067 (0.0054, 0.0081), N0-N1, N0-N2. The values in the H-groups were lower in comparison with the other groups for the androstenedione/DHEA ratio and similar results were found for the androstenedione/DHEAS ratio except for insignificant difference between the H and N0-groups.

Changing 7α-, 7β- and 16α-hydroxylation of Δ⁵-steroids in IgAN patients during the prednisolone treatment

Figure 2A shows the product to precursor ratio reflecting a conversion of DHEA and androstenediol to their 7α-hydroxy-metabolites. This ratio was elevated in IgAN groups and showed an increase at the second stage of GC-therapy of IgAN patients (F=5.14, p=0.014: N0=0.101 (0.085, 0.122), N1=0.094 (0.079, 0.114), N2=0.139 (0.115, 0.173), N0-N2, N1-N2).

Figure 2B shows the product to precursor ratio based on the levels of 7β-hydroxy-DHEA (DHEA7β), 5-androstene-3β, 7β,17β-triol (AT7β), DHEA and androstenediol. This (DHEA7β+AT7β)/DHEA+androstenediol) ratio illustrating a conversion of DHEA and androstenediol to their immunomodulatory 7β-hydroxy-metabolites exhibited a similar picture as in the case of 7α-hydroxylation, except the transient increase during the GC-treatment (F=2.99, p=0.068: N0=0.079 (0.061, 0.105), N1=0.124 (0.0914, 0.176), N2=0.117 (0.087, 0.164), N0-N1).

The 16α-hydroxyprogrenolone/ progrenolone ratio reflecting the 16α-hydroxylation of progrenolone was also elevated in IgAN patients (Fig. 2C). However,
this ratio decreased after GC-application (F=7.82, p=0.002: N0=0.479 (0.393, 0.583), N1=0.366 (0.3, 0.447), N2=0.279 (0.228, 0.34), N0-N2).

Discussion

Reduced activity of adrenal zona reticularis (ZR) in IgAN patients

DHEA is an endogenous antiglucocorticoid serving as a precursor for the synthesis of 30-50% of androgens in men and 100% of estrogens in postmenopausal women (Labrie et al. 1998). At physiological concentrations, this steroid stimulates the interleukin 2 (IL-2) secretion from T helper cells type 1 (Th1) cells but suppresses tumor necrosis factor α (TNFα) and interleukin β (IL1β) production and activation of nuclear transcription factor κB (NF-κB) pathway. DHEA mediates a cytotoxicity induced by T lymphocytes and enhances the natural killer (NK) cell cytotoxicity by stimulation of insulin-like growth factor 1 (IGF-1) production in NK cells. Furthermore, DHEA suppresses type 1 11β-hydroxysteroid dehydrogenase (HSD11B1) mRNA in adipose tissue and promotes the mRNA expression of type 2 11β-hydroxysteroid dehydrogenase (HSD11B2) in renal cells. HSD11B1 metabolite androstenediol, but not the DHEA, protects from viral-induced mortality (Loria 2002). In DHEA, DHEAS, androstenediol and DHEA/pregnenolone ratio, the between-group differences in adrenal androgens showed higher levels in the H-group in comparison with the N0-group, which indicates primarily reduced activity of the adrenal zona reticularis (ZR) in IgAN patients.

Glucocorticoid therapy additionally suppresses adrenal steroidogenesis in IgAN patients including the production of androgens and their immunoprotective 7- and 16α-oxygenated metabolites

The suppression of the hormonal production in zona fasciculata (ZF) by prednisolone therapy was more prominent than the one in ZR as the DHEA/pregnenolone and DHEAS/pregnenolone ratios descended during the prednisolone treatment of IgAN patients. Endogenous GCs but not their synthetic analogues rapidly and dose-dependently stimulated DHEA secretion. Cortisol had no influence on steroid C17-hydroxylase-C17,20-lyase (CYP17A1) but suppressed the activity HSD3B2 activity (Topor et al. 2011). The lack of natural GCs in IgAN patients elevated HSD3B2 activity, which promoted the conversion of adrenal C19-Δ4-steroids to their Δ4-counterparts and consequently reduced the levels of substrates for the synthesis of immunoprotective C19-Δ4-7α/β- and 16α-hydroxy-steroids, the synthesis of which is catalyzed by cytochrome P450 7B1 (CYP7B1), HSD11B1, cytochrome P450 3A4 (CYP3A4) and cytochrome P450 3A7 (CYP3A7). Significant or borderline decrease during the GC-treatment was obvious in all C19-Δ4-steroids.

Increased estradiol levels in IgAN patients irrespectively of GC-therapy and amplified conversion of DHEA to androstenedione in IgAN patients

Adrenal androgens may be peripherally converted to autoimmunity-inducing estradiol (Ahlem et al. 2011a, Ahlem et al. 2011b, Auci et al. 2009, Conrad et al. 2010, Hennebert et al. 2007, Le Mee et al. 2008, Loria 2002, Pettersson et al. 2010, Reading et al. 2012, Tang et al. 2006). However, in spite of reduced synthesis of C19-Δ4-steroids in IgAN patients we surprisingly found higher estradiol levels (independently of GC therapy) when compared with non-IgAN groups (Tables 1 and 2). The estrogen overproduction in IgAN patients may be associated with an amplified conversion of DHEA to androstenedione (catalyzed by HSD3B2) as was observed in these subjects because the androstenedione is a key estrogen precursor (Luu-The 2013). Androstenedione/DHEA and androstenedione/ DHEAS ratios mounted during the GC-therapy and were higher in the T-group when compared with the H-group. We also found a different androstenedione/DHEAS ratio in the U-group when compared with both the H-group (higher values) and the T-group (lower values). Therefore, higher estradiol levels in IgAN groups may be also associated with increased aromatase activity.

Alterations in 7α-, 7β-, and 16α-hydroxylation of Δ4-steroids

The mechanism explaining the immunomodulatory effects of 7α/β- Δ4-steroids may be associated with a competition of 7-oxygenated androstanes for the active sites on the HSD11B1, which catalyzes the conversion of inactive 11-oxy-glucocorticoids to their immunosuppressive 11β-hydroxy-counterparts (Hennebert et al. 2007, Le Mee et al. 2008).

Whereas estradiol induces autoimmunity via estrogen receptors, another mechanism is linked to the catabolism of C19 estrogen precursors such as DHEA, androstenediol, and 5α-androstane-3β,17β-diol (that are...
also estrogenic) to their 7-oxygenated and 16α-hydroxylated catabolites, which cannot be further converted to bioactive estrogens (Pettersson et al. 2010). Androstenediol, even at low concentrations is active on both types of estrogen receptors. The AT7β, which may be either formed by interconversion from the AT7α or directly from androstenediol by the catalytic action of CYP3A4 and CYP3A7, is immunoprotective in spite of its low concentration and high clearance (Ahlem et al. 2011b). The synthetic antinflammatory derivatives of AT7β suppress the production of C-reactive protein interleukin 17 (IL-17), TNFα, interleukin 6 (IL-6) signaling and expression of mRNAs for IL-6 and matrix metalloproteinase in inflamed tissue but intensely stimulate the splenic regulatory T cells and suppress pro-inflammatory cytokines in the lungs (Reading et al. 2012). Estradiol may stimulate the catalytic CYP7B1 activity, mRNA, and human CYP7B1 reporter gene in human embryonic kidney cells HEK293 and may control the DHEA, estradiol, and androstenediol levels in human tissues (Tang et al. 2006). We have demonstrated that DHEA7β, but not DHEA and DHEA7α reduces the immunosuppressive effect of GCs on the formation of plaques in murine spleen lymphocytes (Sterzl et al. 1999). Therefore, the elevated conversion of the C19-Δ^5-steroids to their 7α- and 7β-hydroxy-metabolites (catalyzed by CYP7B1, CYP3A4, CY3A7 and HSD11B1) in IgAN patients may represent a counter-regulatory mechanism compensating the lack of C19-Δ^5 deoxysteroids by amplified synthesis of their more efficient 7-oxygenated (autoimmunity-suppressing) metabolites. The 16α-hydroxylation of pregnenolone (catalyzed by CYP3A4, CYP3A7, CYP7B1) is also higher in IgAN patients. The only difference is the suppression of 16α-hydroxypregnenolone/pregnenolone ratio by GCs.

Possibilities of therapeutic co-application of Δ^5-steroids and glucocorticoids

The C19-Δ^5-steroids mitigate the severity of ADs (Bottasso et al. 2007, Du et al. 2001, Choi et al. 2008, Rontsch et al. 2004, Sudo et al. 2001, Tan et al. 2009) but ADs may weaken the production of adrenal C19-Δ^5-steroids (Bottasso et al. 2007, Kasperska-Zajac et al. 2008). DHEA controls the Th1/Th2 balance and either shifts it towards the Th1 component or attenuates the production of both components (Choi et al. 2008, Romagnani et al. 1998). The C19-Δ^5-steroids also suppress cell-mediated immunity and formation of autoantibodies (Choi et al. 2008, Pratschke et al. 2014, Rontsch et al. 2004, Sudo et al. 2001, Tan et al. 2009). Hence, the co-application of immunosuppressive corticoids with immunoprotective Δ^5-steroids inducing restoration of the Th1-dominated cytokine profile (Hernandez-Pando et al. 1998b) may be favorable for the treatment of ADs. The GC-treatment alone exhibits more than 55% risk for adverse events (Lv et al. 2012) and the therapy exclusively with Δ^5-steroids may be unsafe as well (Hernandez-Pando et al. 1998b). The therapeutic efficiency of androstenediol is higher in comparison with DHEA and the application of adrenal androgens is optimal in an early phase of Th1-mediated response and before the switch to the Th2-mediated stage (Hernandez-Pando et al. 1998a).

Conclusions

The lack of adrenal androgens in IgAN patients might be a consequence of the disease linked to a lower activity of ZR. In addition, there is a further suppression of their synthesis by the GCs. Taking into account the effects of the adrenal androgens, their 7α, 7β, and 16α-hydroxy-metabolites or their stable synthetic derivatives on the early stages of antibody-mediated ADs, the therapeutic co-application of the mentioned substances could be beneficial.

The finding of higher estradiol levels in IgAN patients is important as estradiol stimulates autoimmunity. Therefore, the increased conversion of C19-Δ^5-steroids to their more efficient 7-oxygenated catabolites may be a protective mechanism against the excessive estradiol synthesis.

Conflict of Interest

There is no conflict of interest.

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