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RHINOLOGY

The ratio of 11β-hydroxysteroid dehydrogenase 1/11β-hydroxysteroid dehydrogenase 2 predicts glucocorticoid response in nasal polyps

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Abstract

Background Glucocorticoids are the first-line medical treatment for chronic rhinosinusitis with nasal polyps (CRSwNP), whose local metabolism is catalyzed by 11β-HSD1 and 11β-HSD2. This study investigates the role of 11β-HSD1 and 11β-HSD2 on the glucocorticoid response of CRSwNP patients and the pathogenic mechanism of these polyps.

Methods Forty-three adult CRSwNP patients were enrolled in this study. We evaluated the endoscopic scores by a nasal polyp grading system before and after treatment. We estimated the response to glucocorticoids by the total endoscopic scores. The logistic regression models and inflammatory characteristic curves were conducted to explore the prediction of the response to glucocorticoid in CRSwNP. The expression of 11β-HSD1 and 11β-HSD2 on human sinonasal epithelial cells (HSECS) was measured under the stimulation of toll-like receptor agonists and dexamethasone.

Results The endoscopic scores in the CRSwNP group declined, the expression of 11β-HSD1/11β-HSD2 increased ($r=0.5276$, $P=0.0011$), and the cutoff value of the ratio of 11β-HSD1/11β-HSD2 was 0.4654 (sensitivity 79.17%, specificity 88.89%). Dexamethasone induced a decrease in the ratio of 11β-HSD1/11β-HSD2 ($P=0.049$) by the stimulation of PGN-BS.

Conclusion We found a strong correlation between the response to glucocorticoids and the ratio of 11β-HSD1/11β-HSD2, which could be used as a marker in predicting the level of tissue response to glucocorticoid therapy in CRSwNP. In addition, PGN-BS could also be a therapeutic target, as it is the negative factor that will decrease the sensitivity of glucocorticoids by reducing the ratio of 11β-HSD1/11β-HSD2.

Keywords 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) · 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) · Glucocorticoid sensitivity · Nasal polyps

Abbreviations

11β-HSD1	11β-hydroxysteroid dehydrogenase 1
11β-HSD2	11β-hydroxysteroid dehydrogenase 2
NPA group	Nasal polyps with asthma group
NP-SR group	Nasal polyp sensitivity with glucocorticoids group
NP-CR group	Nasal polyp could not sensitivity with glucocorticoids group

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease characterized by persistent mucosal inflammation with inflammatory cell infiltration, which leads to the clinical symptoms of nasal congestion, rhinorrhea, reduction or loss of smell, headache and facial pain [1, 2]. The symptoms of chronic rhinosinusitis affect the control of some pulmonary diseases such as asthma [3–5]. Meanwhile, Th2-type cytokines, bacteria and viruses all play a role in the pathophysiologic process of patients with CRSwNP [6, 7].

Lijie Jiang and Min Zhou contributed equally to the completion of this article.

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As recommended by the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 [1], glucocorticoids are the first-line treatment for CRSwNP [1]. The action of glucocorticoids is affected by heterogeneity in mechanisms, including the bioavailability of glucocorticoids, which is mainly affected by the expression of 11β-hydroxysteroid dehydrogenase 1(11β-HSD1) and 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) [8, 9]. In 2002, Orsida reported that airway epithelium expressed the two subtypes of 11β-hydroxysteroid dehydrogenase, 11β-HSD1 and 11β-HSD2, which may lead to glucocorticoid insensitivity in treating asthma [10]. Hennebold reported that 11β-HSD1 was lowly expressed in inflammatory cells, such as mast cells, macrophages and dendritic cells [11]. In contrast, the epithelial cells showed higher expression of 11β-HSD1 than the inflammatory cells [12]. In chronic inflammatory conditions, Chapmen reported that dysregulation of 11β-HSD1 and 11β-HSD2 might affect the bioavailability of glucocorticoids [13]. The 11β-HSD1 and 11β-HSD2 expression deregulation may contribute to failure in the treatment of chronic inflammatory disease by inducing intracellular glucocorticoid action in various organs [14–17]. In 2014, Young first reported that nasal sinus mucosa expressed 11β-HSD1 and 11β-HSD2, which might affect the production of endogenous cortisol in human sinus mucosa, and the author also showed that cytokine stimulation could regulate the expression levels of 11β-HSD1 and 11β-HSD2 [18].

Thus, our study aims to investigate the effect of 11β-HSD1 and 11β-HSD2 in the glucocorticoid response in the mucosa from CRSwNP patients. We will further explore the pathogenic mechanism underlying this phenomenon.

Materials and methods

Patients

Forty-three patients with CRSwNP from the First Affiliated Hospital of Sun Yat-sen University were enrolled from April 2016 to June 2017. This study was approved by the local ethics committee ([2016]096), and informed consent was read and signed by all participants. In this study, the presence of nasal polyps (NPs) was confirmed to be bilateral polyps originating from the middle meatus by endoscopic examination and by histopathologic examination. According to the European Position Paper on Rhinosinusitis and Nasal polyps 2012 (EPOS). Serum specific IgEs were measured to evaluate the atopic status. Asthma was diagnosed by pulmonary function test and symptoms of asthma according to Global Initiative for Asthma [19]. All subjects with upper respiratory tract infections or who are allergic to glucocorticoids were excluded. All subjects did not use any other medications (e.g., antibiotics or antileukotrienes) 1 month before starting oral corticosteroid treatment. Patients were orally treated with prednisone at 0.5 mg/kg/day for 1 week according to routine clinical practice, without nasal spray. Their compliance was evaluated by a questionnaire and telephone follow-up, all enrolled patients were confirmed to have taken oral corticosteroid treatment. We found there was no statistical difference in the baseline value of the score between the NP-CR group and NP-SR group (Supplement Fig. 3). Corticosteroid response was evaluated at one week after therapy ended by NP endoscopic score systems (Polyp Grading System), as described previously [20, 21]. Patients who were unable to reduce more than one NP endoscopic score after oral corticosteroid course were considered insensitive to corticosteroids and thus classified as nasal polyps could not respond to glucocorticoids (NP-CR), while patients who reduced more than one NP endoscopic score were classified as nasal polyp sensitivity to glucocorticoids (NP-SR). We collected the clinical characteristics of all patients before and after oral corticosteroid treatment (presented in Table 1). All the subjective symptom scores were analyzed by VAS (Visual Analogue Scale) scores, which included the olfactory hypoesthesia, nasal obstruction, rhinorrhea, and nasal discharge, et al. from the 1 to 10 stages (Supplement Fig. 4).

NP tissues were collected from the nasal cavity of enrolled patients before and after oral corticosteroid therapy to analyze the mRNA and target protein expression. Immunohistochemistry was performed to show the location and expression of the target protein. Nasal epithelial cells were isolated for the in vitro model.

NP epithelial cell isolation and cell culture

Approximately 1 cm × 1 cm NP tissue was collected and washed with Dulbecco's phosphate-buffered saline (DPBS), according to the steps of isolated epithelium cells; it was then plated on cell culture dishes (25 μg/cm^2) in bronchial epithelial growth medium (Lonza, the basal medium included) [22]. The epithelial cells were kept in a 5% CO_2-modified incubator at 37 °C. After a period of approximately 7–10 days, when the density of cells reached 80%, we detected the purity of epithelial cells (> 80%) by flow cytometry. Experiments with primary nasal epithelial cells are shown in E-supplementary Fig. 1.

Real-time PCR

The total mRNA was collected from each sample, as previously reported in detail [23]. The specific primers and probes were predesigned by the Thermo Fisher scientific system, including 11β-HSD1 and 11β-HSD2, and are listed in E-supplementary Table 1. Expression of target genes was normalized to glyceraldehyde-3-phosphate dehydrogenase

Table 1 Clinical characteristics at study for NP-SR and NP-CR groups

	NP-SR	NP-CR	*P* values
Number (*n*)	25	18	–
Age (years, mean ± SD)	39.6 ± 11.29	35.3 ±13.88	–
Sex (M/F)	11/14	8/10	–
Asthma	13/25	4/18	< 0.01
Smokers	4/25	3/18	–
AR	14/25	8/18	< 0.05
Total VAS (mean ± SD)	24.29 ± 9.55	19.78 ± 8.21	–
Bilateral NP endoscopic score before treatment (mean ± SD)	5.94 ± 1.51	5.12 ± 1.30	–
Bilateral NP endoscopic score after treatment (mean ± SD)	4.5 ± 1.65	5.76 ± 1.1	< 0.01
Blood sample			
Proportion of eosinophils (%) (mean ± SD)	0.065 ± 0.062	0.035 ± 0.033	< 0.01
Absolute of eosinophils count (mean ± SD)	0.461 ± 0.365	0.238 ± 0.215	< 0.01
Proportion of NEU (mean ± SD)	4.489 ± 1.609	4.977 ± 1.737	–

NEU neutrophil, *AR* allergic rhinitis, *NPA* nasal polyps with asthma

(GAPDH), and the relative mRNA levels of target genes were analyzed with the $2^{-\Delta\Delta Ct}$ method.

Immunohistochemistry analysis

The NP tissue was fixed and embedded in paraffin, as previously reported, cut into sections, and then stained with hematoxylin. The sections were incubated with rabbit-anti-human monoclonal 11β-HSD2 and polyclonal 11β-HSD1 antibody (Santa) for 12 h at 4 °C. A secondary anti-rabbit and mouse antibody (Dako) was used to incubate the sections for 2 h at 37 °C. The main steps were previously reported in detail [23]. Last, representative photographs were taken by Image Z1.

Western blot

The NP tissue was prepared as previously described. Protein levels of 11β-HSD2 and 11β-HSD1 were evaluated by means of western blot analysis. The relative protein levels were quantified by densitometry image analysis of bands (Bio-Rad Laboratories) and normalized to anti-β-tubulin (Abcam).

Cell stimulation

Human sinonasal epithelial cells (HSECS) were collected from normal control ($n=3$) or NP subjects ($n=5$) (E-supplementary Table 2). HSECS were stimulated by recombinant human IL-4 (rhIL-4), peptidoglycan (PGN-BS), Imiquimod, ultrapure LPS (LPS), polyinosinic-polycytidylic acid [Poly (I:C)], ssRNA40, and dexamethasone as the primary epithelial cell density reached 70–80% for 24 h. The details can be obtained from the methods sections (E-supplementary Fig. 1).

Cortisol levels

Cortisol levels in the bronchial epithelial growth medium of cultured cells were measured using ELISA according to the manufacturer's protocol (R&D systems).

Statistical analysis

Statistical analysis was performed with GraphPad PRISM6 (GraphPad software). Data are presented as the median and square deviation, and the significance was determined with the nonparametric Mann–Whitney *U* test, 2-independent sample *T* tests and Kruskal–Wallis independent test.

The analysis of the relationship between the reduction of NP size and 11β-HSD1, 11β-HSD2 and the ratio of 11β-HSD1/11β-HSD2 in NP tissue was performed using a binary logistic analysis. A linear model was determined. The definition of glucocorticoid sensitivity was defined by NP size reduction. To derive cutoff values for the mRNA expression of 11β-HSD1, 11β-HSD2 and the ratio of 11β-HSD1/11β-HSD2, we constructed receiver operation characteristic (ROC) curves. Analyses were performed using GraphPad PRISM6 (GraphPad software). $P<0.05$ was considered significant (Fig. 1).

Results

The relationship between the ratio of 11β-HSD1/11β-HSD2 and glucocorticoid sensitivity

Forty-three patients with CRSwNP were recruited for oral corticosteroid treatment. Firstly, we defined a decline in polyp scores after 1-week of treatment of less than 1 as

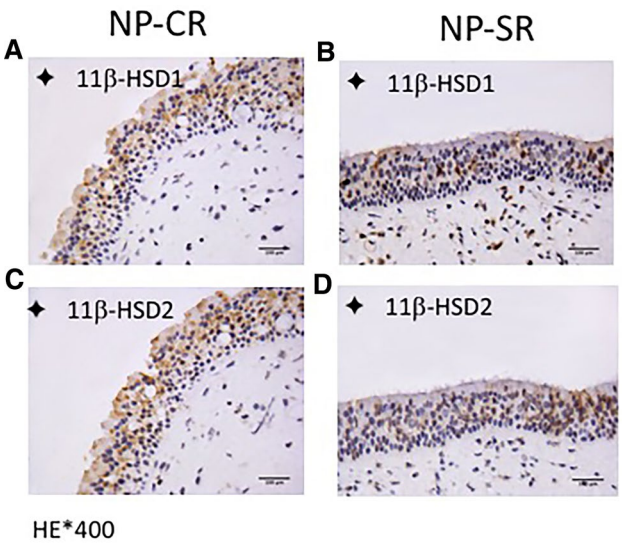

Fig. 1 **a, b** The location and expression of 11β-HSD1 in NP-CR and NP-SR tissue (original magnification ×400); **c, d** The location and expression of 11β-HSD2 in NP-CR and NP-SR tissue (original magnification ×400)

the NP-CR group or the NP-SR group. Before 7 days of treatment, 11β-HSD1 mRNA expression was significantly increased in the NP tissue of the NP-SR group ($n=25$) compared with the NP-CR group ($n=18$) ($P=0.0036$) (Fig. 2a). The cutoff value of the mRNA expression of 11β-HSD1 was 12.2 with a sensitivity of 24% and specificity of 94.44% (AUC 0.722) (Fig. 2b); the 11β-HSD2 mRNA expression in the NP-SR group was significantly decreased compared with the NP-CR group ($P<0.0001$, Fig. 2c). The cutoff value of the mRNA expression of 11β-HSD2 was 0.0430 with a sensitivity of 56% and specificity of 94.44% (AUC 0.844) (Fig. 2d); furthermore, the ratio of 11β-HSD1/11β-HSD2 in the NP-SR group was higher ($n=25$) than in the NP-CR group ($P<0.0001$) (Fig. 2e). The NP scores decreased along with the increase in the ratio of 11β-HSD1/11β-HSD2 ($r=0.5276$, $P=0.0011$). Otherwise, the cutoff value of the ratio of 11β-HSD1/11β-HSD2 was 2.290, with a sensitivity of 79.17% and specificity of 88.89% (AUC 0.866) (Fig. 2f). Second, we defined polyp scores that declined less than 2 as the NP-CR group. Patients in the NP-SR group ($n=19$) had a higher 11β-HSD1/11β-HSD2 gene expression ratio ($P<0.0001$) than those in the NP-CR group ($n=24$), and the cutoff value of the ratio of 11β-HSD1 /11β-HSD2 was 2.290 with a sensitivity of 94.74% and specificity of 86.96% (AUC 0.908) (E-supplementary Fig. 2). ROC curve analysis showed that the glucocorticoid response had high prediction accuracy and the ratio of 11β-HSD1/11β-HSD2 had better effectiveness than the mRNA expression of 11β-HSD1 or 11β-HSD2.

Pro-inflammatory effects on the ratio of 11β-HSD1 /11β-HSD2 in nasal epithelial cells

NP and normal control epithelial cells were isolated from NP or ethmoid biopsy specimens from optic nerve trauma patients and CRSwNP patients. As we know, the bacteria, viral infection and cytokine release from inflammatory cells contributed to aggravating the progression of the disease and affecting the corticosteroids in action. Gram-positive and

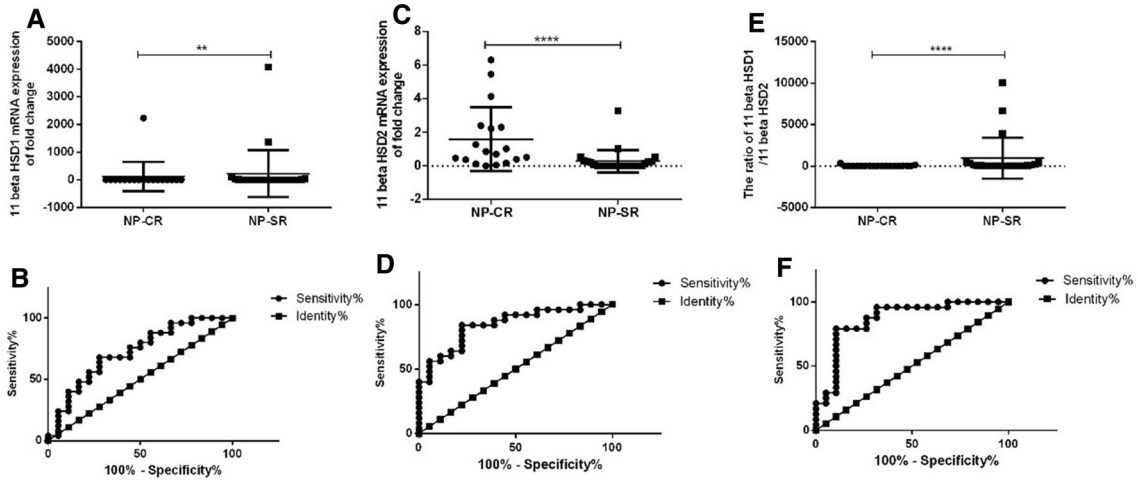

Fig. 2 **a, c, e** The mRNA expression of 11β-HSD1 and 11β-HSD2 and the ratio 11β-HSD1/11β-HSD2 between NP-CR and NP-SR groups; **b, d, f** The prediction models for glucocorticoid response in nasal polyps were tested with the area under the ROC curve: **b** the mRNA expression of 11β-HSD1 was tested with the area under the ROC curve; **d** the mRNA expression of 11β-HSD2 and the ratio of 11β-HSD1/11β-HSD2 between NP-CR and NP-SR groups; **f** the ratio of 11β-HSD1/11β-HSD2 was tested with the area under the ROC curve

Gram-negative bacteria, as well as viral infection, would promote inflammation through TLR activation [24, 25]. TLR2 and TLR4 could be, respectively, activated by Gram-positive peptidoglycan (PGN-BS) and Gram-negative LPS, while TLR3, TLR7, and TLR8 could be activated by Poly (I:C), imiquimod, and ssRNA40, respectively [26–29]. With an in vitro primary HSECS model, rhIL-4 ($P=0.0057$), PGN-BS ($P=0.01$), LPS ($P=0.0057$), and Poly (I:C) ($P=0.002$) significantly increased the mRNA expression of 11β-HSD1 (Fig. 3a) but not 11β-HSD2. Only Imiquimod elevated the mRNA expression of 11β-HSD2 (Fig. 3b). The ratio of 11β-HSD1/11β-HSD2 was significantly elevated by the stimulation of PGN-BS ($P=0.0002$), LPS ($P=0.0002$), and Poly (I:C) ($P=0.0008$) (Fig. 3c).

Anti-inflammatory effects of dexamethasone on the ratio of 11β-HSD1/11β-HSD2 in nasal epithelial cells

Under the stimulation of LPS, rhIL-4, Poly (I:C), imiquimod and ssRNA40, the ratio of 11β-HSD1 /11β-HSD2 showed a rising trend but no significant difference. Only under stimulation of PGN-BS did dexamethasone reduce the ratio of 11β-HSD1/11β-HSD2 ($P=0.049$) (Fig. 4c).

Discussion

Glucocorticoids are recommended as the first-line treatment in CRSwNP [1]. It is important to find a sensitive marker to evaluate the effect of glucocorticoid treatment. 11β-HSD1 and 11β-HSD2 were expressed on nasal epithelium, which could affect the local glucocorticoid activity [18]. 11β-HSD2 is a mineralocorticoid-sensitive glucocorticoid-metabolizing enzyme that could invert the active glucocorticoid to inactive glucocorticoid [30]. We supposed this process might lead to the glucocorticoid insensitivity of CRSwNP. On the other hand, 11β-HSD1 had the opposite function of 11β-HSD2 and could invert the inactive glucocorticoid to active glucocorticoid [16]. In cultured epithelial cells stimulated with dexamethasone, expression levels of 11β-HSD1 were increased compared to nontreated controls, whereas expression levels of 11β-HSD2 were decreased [31]. Se Jin reported that macrolides also increased the expression of 11β-HSD1 in sinonasal epithelium, which contributed to glucocorticoid activation in sinonasal mucosa [32]. The increase of 11β-HSD2 in pulmonary epithelium led to impaired endogenous glucocorticoid activation by the stimulation of IL-13 [33]. In our investigation, the use of the ratio of 11β-HSD1/11β-HSD2 seemed to be more sensitive and specific to predict the glucocorticoid sensitivity in treating CRSwNP than 11β-HSD1 or 11β-HSD2 alone. Considering additional statistics derived from our models, the determined cutoff values for the ratio of 11β-HSD1/11β-HSD2 showed the highest accuracy in predicting glucocorticoid sensitivity in CRSwNP (sensitivity 79.17%, specificity 88.89%). More interestingly, if we defined the polyp score decline of over 2 scores as the NP-SR group, the ratio of 11β-HSD1/11β-HSD2 in patients from the NP-SR group showed higher accuracy in predicting glucocorticoid response in treating CRSwNP (sensitivity 94.74%, specificity 86.96%). However, the shortcoming of our study was the small number of patients recruited ($n=43$). This is the first research

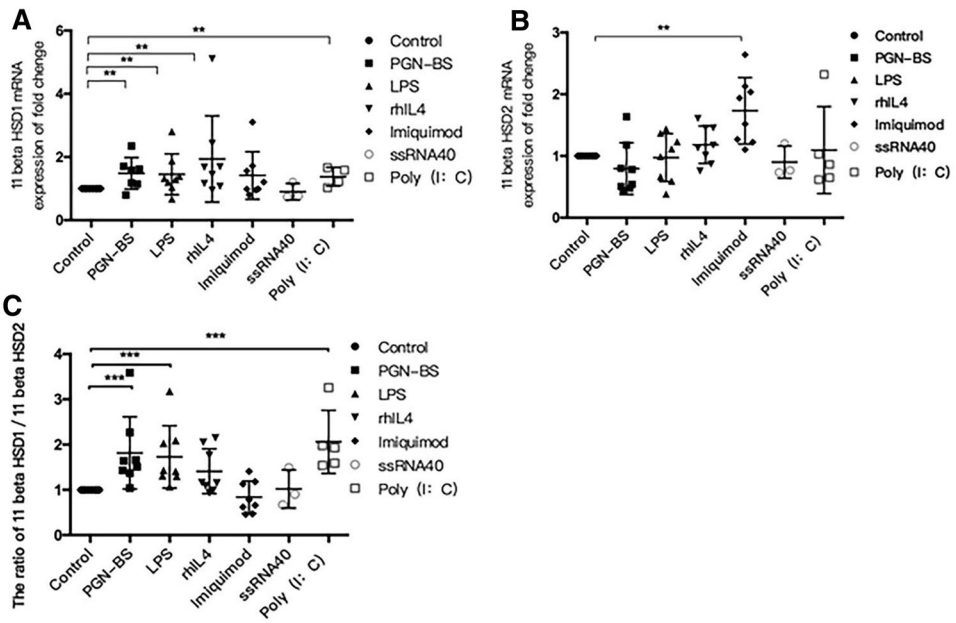

Fig. 3 The epithelial cells under different stimuli: **a** the rhIL-4, PGN-BS,LPS, and poly (I:C) significantly increased the mRNA expression of 11β-HSD1 over the control; **b** Imiquimod elevated the mRNA expression of 11β-HSD2 more than the control; **c** the ratio of 11β-HSD1/11β-HSD2 was significantly elevated under the stimulation of PGN-BS, LPS, and Poly (I:C) compared to the control

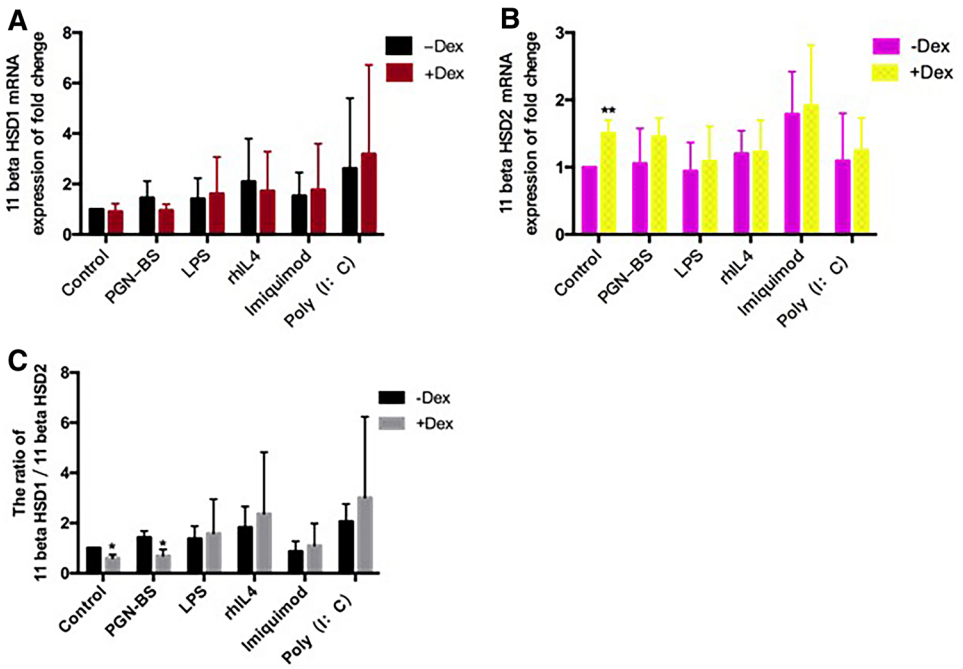

Fig. 4 **a** The effect of dexamethasone on the mRNA expression of 11β-HSD1 under the toll-like receptor agonists (rhIL-4, PGN-BS, LPS, Poly (I:C), and imiquimod) stimulation; **b** dexamethasone increased the mRNA expression of 11β-HSD2 in the control group but did not significantly increase the expression under the toll-like receptor agonists (rhIL-4, PGN-BS, LPS, Poly (I:C), and Imiquimod) stimulation; **c** dexamethasone caused the ratio of 11β-HSD1/11β-HSD2 to decrease by the stimulation of PGN-BS

that revealed the important roles of 11β-HSD1 and 11β-HSD2 in predicting the glucocorticoid response in treating CRSwNP.

Dysregulation of 11β-HSD1 and 11β-HSD2 in chronic inflammatory conditions has been reported. Bryndova reported that 11β-HSD1 was strongly upregulated and 11β-HSD2 downregulated in human and rodent colitis [34]. Additionally, increased 11β-HSD1 activity and mRNA levels were found in synovial tissues of patients with rheumatoid arthritis [35]. Our study showed that TLR2 bacterial agonists (PGN-BS) induced the increasing ratio of 11β-HSD1/11β-HSD2, which could be reversed by the dexamethasone in epithelial cells. We found that rhIL-4, PGN-BS, LPS, and poly (I:C) significantly enhanced the expression of 11β-HSD1 but had no effect on 11β-HSD2. Otherwise, under the stimulation of imiquimod, 11β-HSD2 significantly increased compared with controls. Our study first demonstrated that the expression of two isolates of glucocorticoid-metabolizing enzymes could be affected by the production of bacteria and viruses and found that imiquimod, the TLR7 agonist, could markedly increase the expression of 11β-HSD2.

Conclusions

We found a strong correlation between the response to glucocorticoids and the ratio of 11β-HSD1/11β-HSD2, which could be used as a marker for predicting the level of tissue response to glucocorticoid therapy in CRSwNP. In addition, PGN-BS could also be a therapeutic target, as it is the negative factor that will decrease the sensitivity of glucocorticoids by reducing the ratio of 11β-HSD1 /11β-HSD2.

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Compliance with ethical standards

Conflict of interest The authors have declared that there is no conflict of interest.

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