



Cloning of chicken 11 β -hydroxysteroid dehydrogenase type 1 and its tissue distribution

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ARTICLE INFO

Article history:

Received 10 July 2007

Accepted 6 June 2008

Keywords:

11 β -Hydroxysteroid dehydrogenase
Short-chain dehydrogenase/reductase
Glucocorticoid metabolism
Birds

ABSTRACT

11 β -Hydroxysteroid dehydrogenase type 1 (11HSD1) is an enzyme that interconverts active 11-hydroxy glucocorticoids (cortisol, corticosterone) and their inactive 11-oxo derivatives (cortisone, 11-dehydrocorticosterone). Although bidirectional, it is considered to operate *in vivo* as an 11-reductase that regenerates active glucocorticoids and thus amplifies their local activity in mammals. Here we report the cloning, characterization and tissue distribution of chicken 11HSD1 (ch11HSD1). Its cDNA predicts a protein of 300 amino acids that share 51–56% sequence identity with known mammalian 11HSD1 proteins, while in contrast to most mammals, ch11HSD1 contains only one N-linked glycosylation site. Analysis of the tissue distribution pattern by RT-PCR revealed that ch11HSD1 is expressed in a large variety of tissues, with high expression in the liver, kidney and intestine, and weak in the gonads, brain and heart. 11-Reductase activity has been found in the liver, kidney, intestine and gonads with low or almost zero activity in the brain and heart. These results provide evidence for a role of 11HSD1 as a tissue-specific regulator of glucocorticoid action in non-mammalian vertebrates and may serve as a suitable model for further analysis of 11HSD1 evolution in vertebrates.

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1. Introduction

Glucocorticoids are steroids that mediate important diverse physiological effects in vertebrates from fish to mammals including human. They are synthesized and secreted by adrenal cells and are regulated by adrenocorticotrophic hormone whose release is under the control of the hypothalamic–pituitary–adrenal axis. Local action of glucocorticoids depends on various processes such as passage through the cell membrane, binding to the glucocorticoid receptors, specific interaction of receptor–ligand complex with genes bearing glucocorticoid response element or with other transcription factors, and on intracellular metabolism that controls the number of biologically active molecules in the target cells.

It is well known that the physiological functions of glucocorticoids are lost when the hydroxyl group at C₁₁ is oxidized to an oxo group, and likewise active glucocorticoids are regenerated by reduction of the oxo group at C₁₁. The enzyme that is responsible for these activities is 11 β -hydroxysteroid dehydrogenase, 11HSD [1,2]. This enzyme is a product of two distinct genes that belong to the large superfamily of short-chain dehydrogenases/reductases (SDR) that have the conserved

dinucleotide-binding site and the conserved but variable motif responsible for the orientation of the substrate and the catalysis of proton transfer to and from reduced and oxidized reaction intermediates [3]. The 11HSD type 1 is a NADP⁺(H)-dependent bidirectional enzyme that functions predominantly as a reductase *in vivo*. It converts the biologically inactive 11-oxo glucocorticoids cortisone and 11-dehydrocorticosterone to their active 11-hydroxy derivatives cortisol and corticosterone. In contrast, the type 2 isoform (11HSD2) is a unidirectional NAD⁺-dependent dehydrogenase that inactivates biologically active glucocorticoids [1,2]. Thus, 11HSD2 inactivates intracellular glucocorticoids, whereas 11HSD1 regenerates active glucocorticoids from their 11-oxo derivatives and amplifies local glucocorticoid action. It is evident that the spatial and temporal regulation of the expression of both enzymes is an important determinant of the glucocorticoid response.

11HSD2 was cloned and its physiological functions were studied not only in mammals [1,3] but also in some non-mammalian species [4–7] and the data suggest that 11HSD2 function is conserved during evolution. Unlike 11HSD2, 11HSD1 occurrence and its evolutionary conservation in non-mammalian vertebrates are unclear. To investigate whether 11HSD1 is also conserved throughout vertebrate evolution we used chicken genome sequence resources to identify 11HSD1 gene for comparative analyses of avian and mammalian 11HSD1 and for expression pattern of avian enzyme in chicken tissues.

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2. Materials and methods

2.1. Animals

Experiments were performed on 5–7-week-old Brown Leghorn chickens obtained from the hatchery of the Institute of Molecular Genetics (Czech Acad. Sci., Prague) fed a commercial poultry diet. The birds were killed by decapitation and exsanguination and various tissues were quickly removed. To study the expression and activity of 11HSD1 in the oviduct, some chickens were treated daily with an s.c. injection of 2 mg diethylstilbesterol (DES) per kg in polypropylene glycol for 7 days starting from day 22. The animal protocol was approved by the Institutional Animal Care Committee.

2.2. Chicken 11HSD1 sequence identification and verification

Based on a comparison of the high sequence homology among the known sequences of 11 β HSD1 in mammals (human, squirrel monkey, guinea pig, rabbit, rat, mouse, hamster and sheep), the predicted mRNA sequence of this enzyme in chickens was constructed using the program CLUSTAL W. Briefly, the known sequences were used to search chicken EST (expressed sequence tags) in the free internet NCBI database for cDNA fragments with the highest similarity. The fragments found were used to further search the database for other overlapping fragments and thus elongate the sequence.

The generated sequence of more than 1031 bp was searched for an open reading frame by the Basic Local Alignment Search Tool. Based on the sequences of putative ch11HSD1, the ORF-specific forward and reverse primers were designed by the program Lasergene (DNASTAR, Madison, WI) (Table 1) and used in the subsequent PCR. Total RNA was isolated from chicken liver by RNA Blue (Top Bio, Prague, Czech Republic), cDNA was synthesized from 5 mg of RNA by reverse transcription with oligo(dT) primers (Sigma, St. Louis, MO) and M-MLV Reverse Transcription Reagents (Invitrogen), and the synthesized cDNA with ORF-specific primers were used to obtain the 11HSD1 amplicon. The PCR reaction mixture contained 2.5U of Platinum Tag polymerase, 20 pmol of both the sense and antisense primers, 200 μ M dNTPs, 50 mM KCl, 15 mM Tris-HCl, 0.5 mM MgCl₂, and 1 μ l of chicken cDNA. Liver cDNA was used to amplify the 11HSD1 amplicon, since Monder and Lakshmi [8] showed that avian liver reduces 11-dehydrocorticosterone to corticosterone. All PCR products were separated on 1% agarose gel and isolated using a GenElute Gel extraction kit (Sigma). Subsequently, the isolated cDNA fragments were inserted into the pGEM Easy Vector System (JM 109 competent cells; Promega), the plasmid DNA was purified with a QIAprep Spin Miniprep kit (Qiagen) and sequenced by the ABI PRISM 3100 DNA sequencer in the Academy of Sciences Sequencing Facility. The obtained sequences were compared with predicted transcripts downloaded from www.ensembl.org (predicted 11HSD1

Table 1
ORF-specific primers and primers used for semi-quantitative real time RT-PCR

Gene	Sense (5' → 3')	Antisense (5' → 3')
ORF-specific primers		
11HSD1	TCCCTGGCCACGCATCTGCTCC	GGCATTGCTTCAGGGT GGGCTTTTC
Semi-quantitative PCR primers		
11HSD1	AGGGCAACATTGTGGTGGTCTCAT	CTGGGCTGGCGGT GGTCTCTT
β -actin	TGATATTGCTCGCTCGTTGTTGA	CATGGCTGGGGTGT GAAGTCTC

ID: ENSGALT0000002088) and matching regions were used to design real-time PCR primers (Table 1) using the program Lasergene.

The open reading frame was translated into the protein sequence and the 3D model was constructed using the known human sequence as a template. The human 11HSD1 structure model was obtained from the RCSB Protein Data Bank (Research Collaboratory for Structural Bioinformatics): PDB ID 1XU7. 3D models were created using the DeepView application of the SWISS-MODEL Automated Comparative Protein Modeling Server (www.expasy.org).

2.3. Analysis of ch11HSD1 gene expression

Total RNA from various tissues was extracted by RNA Blue. cDNA was synthesized from 5 μ g RNA using M-MLV Reverse Transcriptase reagents and oligo(dT). Amplification of the target cDNA was performed in LightCycler using LightCycler FastStart DNA Master SYBR Green I and primers designed with the program Lasergene (DNASTAR, Madison, WI) (Table 1). Relative concentrations were calculated from crossing points using the standard curve method. Expression of the target genes was normalized to β -actin and to total RNA.

2.4. 11HSD1 enzymatic assay

The activity of 11HSD1 was studied in tissue slices and homogenates. Tissues were homogenized (1:9, w/v) in ice-cold buffer containing 200 mM sucrose and 10 mM TRIS/HCl (pH 8.5) with a Polytron homogenizer. The homogenates were centrifuged at 1000 \times g for 10 min and the supernatant was assayed for protein concentration using the Bradford Coomassie blue method. The 11-reductase activity was assayed in tubes containing buffer (100 mM KCl, 50 mM TRIS/HCl, pH 8.5), cosubstrate (0.8 mM NADPH), and substrate (35 nM [³H]11-dehydrocorticosterone). Experiments were performed in the presence of 1 mM glucose-6-phosphate and 2U glucose-6-phosphate dehydrogenase to regenerate NADPH [9]. The amounts of protein and incubation times were optimized to ensure the linearity of enzymatic reaction.

The tissue slices were prepared and their metabolism analyzed as described previously [6,10]. Briefly, freshly removed tissues were washed in ice-cold 150 mM NaCl, cut into slices less than 1 mm thick and placed in tubes containing preheated and oxygenized DMEM, 0.8 mM NADPH and 35 nM [³H]11-dehydrocorticosterone. The tubes were gassed with 95% O₂/5% CO₂, stoppered and incubated at 37 °C in a shaking water bath. The incubation time for each tissue was determined by pilot experiments.

The reactions were halted by cooling, unlabelled corticosterone or 11-dehydrocorticosterone was added and the steroids extracted with SepPak cartridges (Waters, Milfors, MA, USA). After the evaporation of methanol under nitrogen, the steroids were separated and quantified by HPLC with on-line detection using a flow-cell detector (Radiomatic 150TR, Canberra Packard, Meriden, CT, USA) as mentioned earlier [11]. Activities were expressed as pmol of converted substrate per hour and mg of protein (homogenate) or per mg of dry weight (tissue slices). The corticosteroids 11-dehydrocorticosterone (4-pregnen-21-ol-3,11,20-trione), corticosterone (4-pregnen-11 β ,21-diol-3,20-dione), 20-dihydroprogesterone (4-pregnen-11 β ,20 β ,21-triol-3-one), and 11-dehydro-20-dihydrocorticosterone (4-pregnen-20 β ,21-diol-3,11-dione) were purchased from Steraloids (Newport, RI). [³H]11-dehydrocorticosterone was prepared from [³H]corticosterone using 11HSD2 from guinea pig kidney.

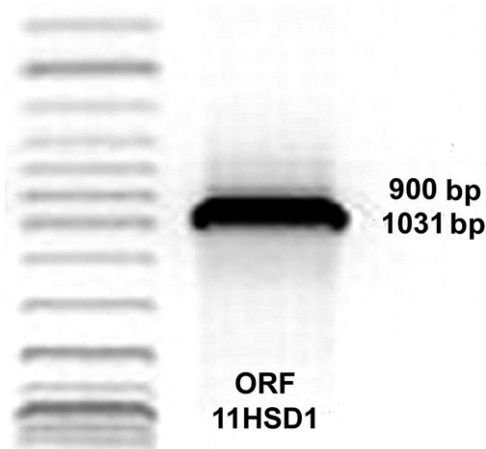


Fig. 1. Electrophoresis of PCR product of putative ORF of 11HSD1 using primers mentioned in Section 2.

3. Results

3.1. Chicken 11HSD cDNA and its deduced primary structure

The strategy to identify putative chicken 11HSD1 was based on a search of the chicken EST database for the cDNA fragments with the highest similarity to the conserved regions of this enzyme in mammalian species. The identified fragments were then used to further search the database for other overlapping fragments to elongate the sequence. Based on these sequences, primers were designed to characterize the full-length open reading frame (ORF). As shown in Fig. 1, the 1031-bp amplified product was identified and this length of the amplified ORF fragment for 11HSD1 was identical to the deduced fragment (Fig. 2). The nucleotide sequence of ch11HSD1 was deposited in the EMBL nucleotide sequence database under the accession number ENSGALT00000002088.

Fig. 3 displays the deduced amino acid sequences of putative ch11HSD1, together with a comparison to other currently known 11HSDs. The deduced ch11HSD1 encodes a protein of 300 amino acids. A sequence comparison (Table 2) revealed 51–56% identity of ch11HSD1 with that from mammals. Similar to other enzymes of the SDR family [12], ch11HSD1 contains the catalytically active triad consisting of tyrosine and lysine residues (Tyr-X-X-Lys) and serine 14 residues upstream, amino acids important for catalytic activity, and the conserved glycine-rich N-terminal cosubstrate-binding site (Gly-X-X-X-Gly-X-Gly). ch11HSD1 contains one potential glycosylation site with the Asn-X-Ser consensus sequence motif located at amino acid residues 207–209. The structural features of ch11HSD1 are very similar to the human enzyme (Fig. 4).

3.2. Tissue distribution of 11HSD1 mRNA

When total RNA from a range of various tissues was analyzed by RT-PCR with the primers shown in Table 1, a single 407 bp mRNA was detected in all tissues using electrophoretic analysis of the reaction product (not shown). 11HSD1 transcription was relatively high in the liver, kidney and intestine whereas low levels were found in the oviduct, heart, brain and gonads (Fig. 5). Expression of the target genes was normalized to β -actin and to total RNA since the usefulness of normalization against the β -actin gene in various tissues is limited [13].

3.3. Tissue distribution of 11HSD1 activity

11-Reductase activity was found in both homogenates and slices of various chicken tissues and survey of these activities is presented in Fig. 6. Chromatographic analysis of the incubation products revealed not only corticosterone, 20-dihydrocorticosterone and 11-dehydro-20-dihydrocorticosterone but also two other unknown slower moving metabolites, that were detected not only in slices but also in homogenates when the NADPH-regenerating system was used. One of the unknown metabolites was found in liver whereas the other in the ovary, brain and heart. We propose that one of them might be tetrahydro-11-dehydrocorticosterone, as Monder and Lakshmi [8] showed that 11-dehydrocorticosterone is reduced to both corticosterone and tetrahydro-11-dehydrocorticosterone in the livers of various avian species. In addition, it was recently demonstrated that the deactivation of 11-dehydroglucocorticoids via 5 α -reductase is an important metabolic pathway in the liver [14] and 3 β -hydroxysteroid dehydrogenase was detected in chicken tissues [15].

If corticosterone instead of 11-dehydrocorticosterone was used in the same assay as a substrate, neither of the unknown metabolites was found. In the liver only 20-dihydrocorticosterone was observed, whereas in the kidney, intestine, gonads and oviduct 20-dihydrocorticosterone, 11-dehydro-20-dihydrocorticosterone and 11-dehydrocorticosterone were found (data not shown).

4. Discussion

This is the first determination of the nucleotide sequence of a non-mammalian cDNA encoding 11HSD1. The cloned chicken 11HSD1 cDNA (ch11HSD1) predicts a protein of 300 amino acids, which is longer than most mammalian species by 8 amino acids. The predicted amino acid sequence of ch11HSD1, when aligned with the known mammalian enzymes, revealed a similarity of about 51–56%, but the putative cosubstrate-binding site and active site were highly conserved and had much higher similarity to that of mammals. Comparison of the cosubstrate-binding site of ch11HSD1 showed a very high homology with mammals, only two semi-conservative substitutions of serine and arginine for lysine were found.

Table 2

Protein sequence homology of chicken 11HSD1 with known sequences of mammals, expressed in percentage of identical amino acid residues

	Chicken	Sheep	Guinea pig	Hamster	Mouse	Rat	Rabbit	Squirrel monkey
Human	56	78	73	78	78	76	80	91
Squirrel monkey	54	74	72	75	75	75	79	X
Rabbit	54	74	72	75	75	74	X	79
Rat	51	72	73	77	87	X	74	75
Mouse	53	75	73	79	X	87	75	75
Hamster	53	75	73	X	79	77	75	75
Guinea pig	52	72	X	73	73	73	72	72
Sheep	54	X	72	75	75	72	74	74

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11βHSD1      AACGGAGGCCAAGCTGCAGAAGGTAGTGGAAAAGTGCCTGGATCTGGGTGCTGCATCTGC 300
predicted11βHSD1 -----GTAGTGGAAAAGTGCCTGGATCTGGGTGCTGCATCTGC 38
                *****

11βHSD1      CCGCTATGTGAGCGGCTCCATGGAGAGCACAGCCTTTGCTGAGGAGGTGGTCAAAGAGGC 360
predicted11βHSD1 CCGCTATGTGAGCGGCTCCATGGAGAGCACAGCCTTTGCTGAGGAGGTGGTCAAAGAGGC 98
                *****

11βHSD1      TGAGAACATCTGGGGAGGCCTCGACATGCTCATCCCGAACCACATCGGCCGCAGCTTTTT 420
predicted11βHSD1 TGAGAACATCTGGGGAGGCCTCGACATGCTCATCCTGAACCACATCGGCCGCAGCTTTTT 150
                *****

11βHSD1      TGACTTCTTCAACGGGGACGTGGATCACGTGCGGAAGCTCATGGAGACCAACTTCTCAG 480
predicted11βHSD1 TGACTTCTTCAACGGGGACGTGGATCACGTGCGGAAGCTCATGGAGACCAACTTCTCAG 218
                *****

11βHSD1      CTACGTGGCCATGACCACGTCCGCCCTGCCCATGCTGAAGGAGAGTGAGGGCAACATTTGT 540
predicted11βHSD1 CTACGTGGCCATGACCACGTCCGCCCTGCCCATGCTGAAGGAGAGTGAGGGCAACATTTGT 278
                *****

11βHSD1      GGTGGTCTCATCTGTTTCAGGTAAGTCGCCTCCCCCTTCGTTGCTCCCTACTCTGCAAC 600
predicted11βHSD1 GTGGTCTCATCTGTTTCAGGTAAGTCGCCTCCCCCTTCGTTGCTCCCTACTCTGCAAC 338
                *****

11βHSD1      TAAGTTTGCCTTGGAAGGATTCTCAGCTCCCTGAGGCATGAATTCATCATAGAAAAGGT 660
predicted11βHSD1 TAAGTTTGCCTTGGAAGGATTCTCAGCTCCCTGAGGCATGAATTCATCATAGAAAAGGT 398
                *****

11βHSD1      CAATGTTTCCATCAGCTCTGCATCTTGGGCTATATTAACACAGAGAACCGGGTGCAGAT 720
predicted11βHSD1 CAATGTTTCCATCAGCTCTGCATCTTGGGCTATATTAACACAGAGAACCGGGTGCAGAT 458
                *****

11βHSD1      GGTCTCACACATCATTAAGGAAGCACCAGCACCCAAGGAGGAGTGTGCGCTGGAGATCAT 780
predicted11βHSD1 GGTCTCACACATCATTAAGGAAGCACCAGCACCCAAGGAGGAGTGTGCGCTGGAGATCAT 518
                *****

11βHSD1      CCGGAGTGGGGCCCTGCGGCAGCGTGAGCTGCACTACCCCTGCCAGCACCGTGACCCCAAC 840
predicted11βHSD1 CCGGAGTGGGGCCCTGCGGCAGCGTGAGCTGCACTACCCCTGCCAGCACCGTGACCCCAAC 578
                *****

11βHSD1      GCTGCTGCTGCGGGACCTTGCTCCCGAGTTTCTGGATGGCCTCATCAGGAACAACATGCG 900
predicted11βHSD1 GCTGCTGCTGCGGGACCTTGCTCCCGAGTTTCTGGATGGCCTCATCAGGAACAACATGCG 638
                *****

11βHSD1      GGTGGAAAACATCAAGAGACCACCGCCAGCCCAGGGCTCGGGGCATTAGCACAGCTCTGA 960
predicted11βHSD1 GGTGGAAAACATCAAGAGACCACCGCCAGCCCAGGGCTCGGGGCATTAG----- 687
                *****

11βHSD1      GTGGCCAACGCTTCCCCATGGGCAGTGGTGCCTCCAGAAAAGCCCACCCTGAAGCAATGC 1020
predicted11βHSD1 -----

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Fig. 2. Nucleotide sequence of chicken 11HSD1 cloned by PCR with predicted nucleotide sequence. Numbers to the right correspond to the nucleotide sequence. (*) Indicates identical nucleotides in cloned and predicted sequence. The primers designed for semi-quantitative real time RT-PCR are written in bold.

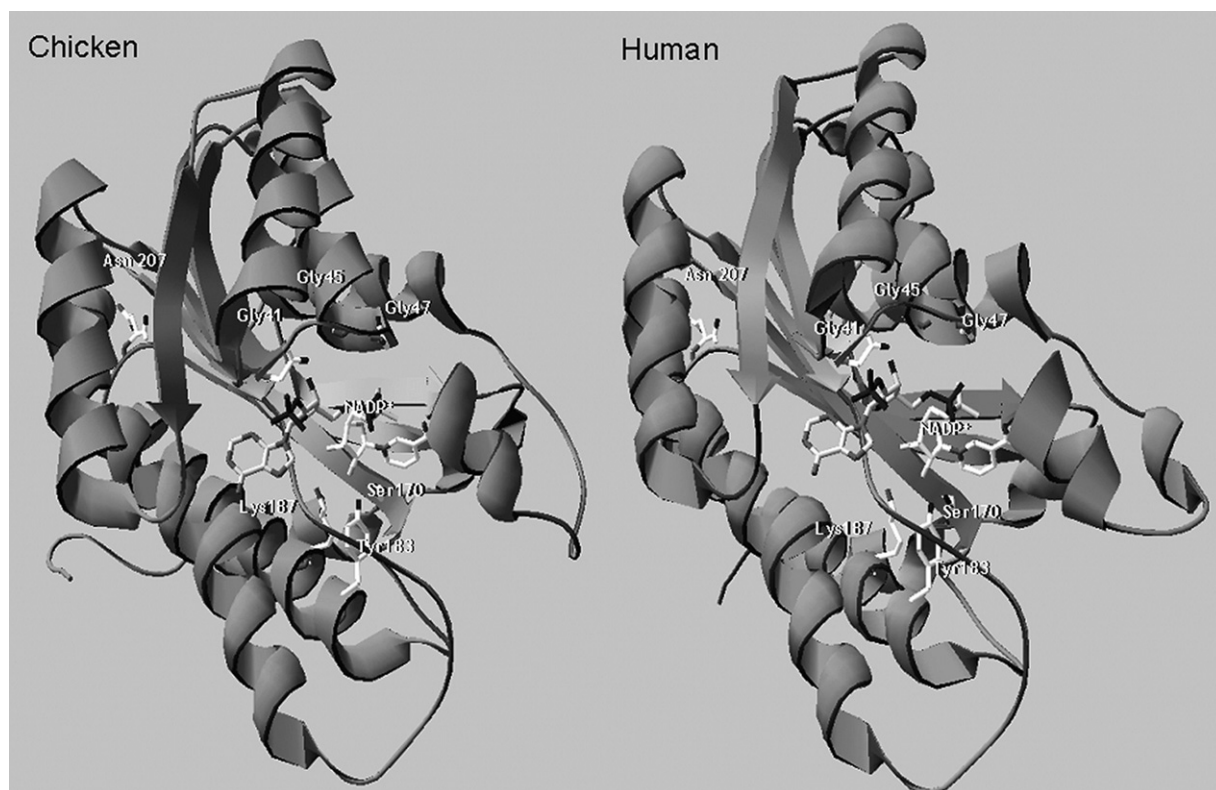


Fig. 4. Schematic representation of the structural features of human and chicken 11HSD1. This figure was generated using the program DeepView.

11HSD1 belongs to the short-chain dehydrogenase/reductase superfamily of $\text{NAD}^+(\text{H})/\text{NADP}^+(\text{NADPH})$ -dependent oxidoreductases. These enzymes are characterized by a cosubstrate-binding site near the N-terminal part of the molecule involving a structurally conserved Rossmann fold and the Gly-X-X-Gly-X-Gly motif. Other strictly conserved residues are the tyrosine and lysine located 4 residues downstream. The Tyr-X-X-X-Lys segment is assigned to the catalytic center together with the serine 14 residues upstream. These residues are responsible for the orientation of the substrate via hydrogen bonding with the hydroxyl group (serine) and for proton transfer between the oxidized and reduced intermediates (tyrosine, lysine) [12,16]. In this study we have shown that putative ch11HSD1 shares the conserved motifs of the SDR superfamily and that the model of tertiary structure corresponds well to the human 11HSD1 enzyme, whose X-ray coordinates are available [17]. In addition, deduced ch11HSD1 also contains a potential glycosylation site with an Aspn-X-Ser sequence motif. In contrast to mammalian 11HSD1, which usually contains two (rat) or three (human, rabbit) potential glycosylation sites [18,19], the ch11HSD1 molecule contains only one site. The absence of the first and second glycosylation site from the deduced ch11HSD1 protein is similar to guinea pigs [20]. Considering that the third site is essential for the activity of 11HSD1 in some [18] but not all mammalian 11HSD1s [21], the chicken enzyme with only one glycosylation site provides a further protein for studies of the role of carbohydrates in maintaining an active 11HSD1 molecule. Preliminary studies with expression of ch11HSD1 in *E. coli* indicate that glycosylation might be important for proper function of the enzyme.

The physiological role of 11HSD1 in mammals is very broad and seems to be also intricately involved in the pathogenesis of various diseases. Though this enzyme is bidirectional, *in vivo* it is believed to operate as a reductase generating biologically active glucocorticoids, cortisol and corticosterone, from their biologically inactive

11-oxo derivatives, cortisone and 11-dehydrocorticosterone. As it is distributed in mammalian tissues inhomogeneously, 11HSD1 functions as a tissue-specific regulator of the glucocorticoid response [2]. To gain insight into the functional significance of this enzyme in chicken, we characterized the distribution of ch11HSD1 mRNA and activity in various tissues. Our data show that the distribution of ch11HSD1 transcription is broadly similar to that of mammals. ch11HSD1 mRNA is highly expressed in the kidney, liver and intestine. Similarly, high levels of 11HSD1 transcription and protein were also found in mammalian kidney, liver and intestine [2], where

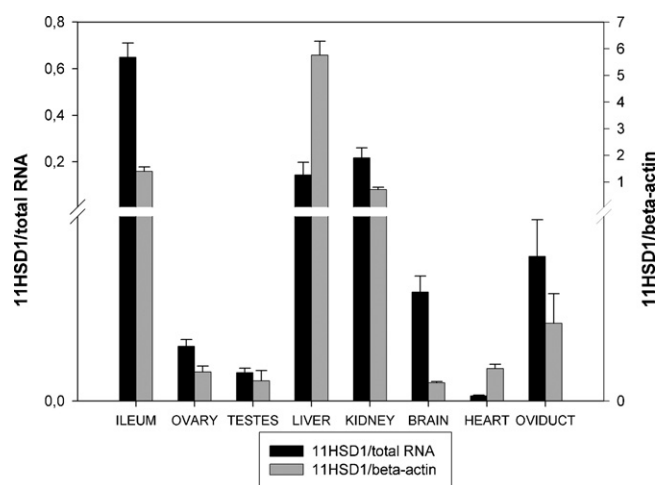


Fig. 5. Tissue distribution of chicken 11HSD1 mRNA. Relative levels of ch11HSD1 expression were normalized to total RNA or β -actin. The ch11HSD1 mRNA abundance in the oviduct was measured in chicks treated with DES (for further details, see Section 2). Values are means \pm S.E.M. of 5–10 animals.

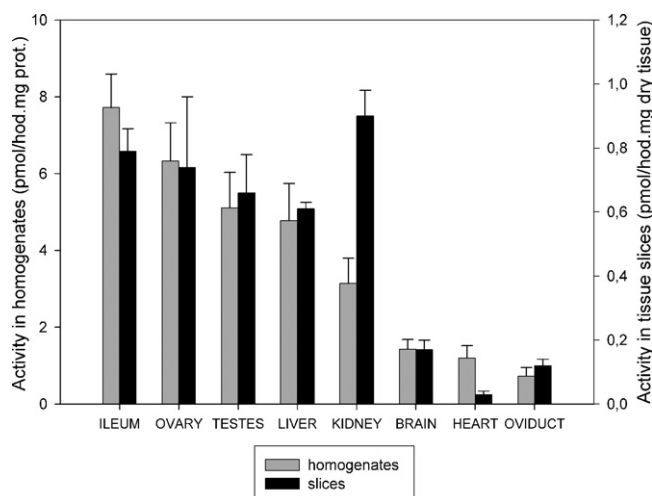


Fig. 6. Reduction of 11-dehydrocorticosterone to corticosterone in tissue slices and homogenates. 11HSD1 reductase activity was calculated as the conversion of 11-dehydrocorticosterone to corticosterone per hour and milligram of dry weight (slices) or of protein (homogenates). Activity in the oviduct was measured in chicks treated with DES (for further details see Section 2). Values are means \pm S.E.M. of 7 animals.

11HSD1 is not expressed in enterocytes [22] but in the subepithelial layer, in particular in immune cells [23] and fibroblasts [24]. The low level of ch11HSD1 expression in the heart and brain is probably due to the fact that this enzyme is expressed only in some cell types, such as interstitial fibroblasts of the endocardium but not in myocytes [25] and only in some brain regions such as the cerebellum and hippocampus [26,27]. The low levels of ch11HSD1 transcript in the gonads is surprising, because mammalian gonads express appreciable levels of this enzyme [2] and we have seen high level of 11-reductase activity in chicken gonads. The differences between these studies probably reflect the problem with normalizing the ch11HSD1 transcript level, the presence of other carbonyl reductases that convert 11-dehydrocorticosterone to corticosterone, or the fact that we used sexually immature birds. Recent studies in mammalian ovaries have shown that 11HSD1 is expressed in developing oocytes and luteinized theca cells whereas 11HSD2 is expressed in the preovulatory stage [28].

The demonstration of several metabolites of 11-dehydrocorticosterone in various organs suggests that several other steroid metabolizing enzymes are present, and not just 11HSD1. One of them is 3,20-hydroxysteroid dehydrogenase, which we have recently cloned and identified in many chicken tissues [29]; the other seems to be 5 α -reductase, which was identified in avian liver by Monder and Lakshmi [8]. The co-existence of several steroid enzymes that need NADPH as a cosubstrate may be of great physiological importance, because liberated NADP⁺ from the reaction catalyzed by 5 α -reductase may hinder 11HSD1 reductase activity. In addition, the conversion of 11-dehydrocorticosterone to tetrahydro-derivatives can limit the actual capacity of the cellular metabolism to reactivate corticosterone from biologically inactive 11-dehydrocorticosterone.

In conclusion, our study demonstrates the presence of 11HSD1 in chicken and represents the first identification of 11HSD1 in a non-mammalian genus. Based on the sequence homology with mammalian 11HSD1s and distribution of ch11HSD1 mRNA and 11-reductase activities in various tissues, ch11HSD1 resembles the putative avian enzyme. Similar to mammals, avian 11HSD1 is expressed in a wide distribution among various tissues and thus this enzyme might operate as a tissue-specific regulator of the glucocorticoid response.

Acknowledgements

This work was supported by the Academy of Sciences of the Czech Republic (grant nos. IAA 6011201 and AVOZ 50110509). The authors would like to thank Miss I. Mezteková and Mrs. I. Muricová for their skilful technical assistance.

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