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Cloning, Sequencing and Tissue-distribution of Mouse 11β-hydroxysteroid Dehydrogenase-1 cDNA

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11β-Hydroxysteroid dehydrogenase (11β-HSD) reversibly converts physiological glucocorticoids (cortisol, corticosterone) to inactive 11-dehydro forms, and thus controls glucocorticoid access to receptors in a variety of tissues. We have cloned a cDNA encoding 'liver-type' 11β-HSD (11β-HSD1) from the mouse using PCR, and have determined its nucleotide sequence. Mouse 11β-HSD1 cDNA showed 91% identity to rat 11β-HSD1 cDNA. There was 87% amino acid identity with rat 11β-HSD1 with conservation of the putative cofactor and substrate binding domains. Northern blot analysis of mouse tissues demonstrated abundant 11β-HSD1 message in the liver, kidney and lung, with lower expression in brain subregions and gonads. 11β-HSD1 mRNA was below the level of detection in the murine colon. 11β-HSD1 mRNA levels in kidney was higher in males than in females, but in contrast to the rat, there was no sexual dimorphism in the mouse liver. Although males and females showed different mRNA levels in the kidney, there was no sex difference in 11β-HSD enzyme activity. Thus, despite the high inter-species conservation of 11β-HSD1, there are clear species and tissue-specific differences in its expression.

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INTRODUCTION

11β-Hydroxysteroid dehydrogenase (11β-HSD) catalyses the reversible conversion of active glucocorticoids (cortisol in man, corticosterone in rats and mice) to their inactive 11-dehydro forms (cortisone and 11-dehydrocorticosterone, respectively), thus controlling the access of glucocorticoids to intracellular corticosteroid receptors [1–4]. Biochemical evidence indicates the existence of at least two distinct forms of 11β-HSD, one with a higher K_m (μM) for its glucocorticoid substrates and a preference for $NADP^+$ as cofactor (11β-HSD1) or 'liver-type' 11β-HSD [5], and a second (11β-HSD2) with a lower K_m (nM) and preference for NAD^+ as cofactor [6, 7]. The higher affinity 11β-HSD2 isoform appears to be important in mineralocorticoid target tissues including the distal nephron where it confers aldosterone selectivity upon otherwise non-selective mineralocorticoid receptors [6] and also in placenta [7] where it may function to exclude maternal glucocorticoids from the foetus [reviewed in 4]. 11β-HSD1 may be involved in regulating the access of glucocorticoids to both glucocorticoid and mineralocorticoid receptors in a wide variety of tissues including the liver [8], brain [9, 10] and vasculature [11] and in the hepatic regeneration of active glucocorticoids from inactive circulating 11-keto metabolites [12].

A cDNA encoding 11β-HSD1 has been cloned from a rat liver expression library using antibodies raised to the 11β-HSD1 protein purified from rat liver microsomes [13]. Subsequently, cDNAs encoding 11β-HSD1 have been cloned from human, sheep and squirrel monkey [14–16] and genomic sequences encoding 11β-HSD1 have been isolated from human and rat [14, 17]. Comparison of the nucleotide sequences of these cDNAs shows a high degree of conservation across species. Analysis of 11β-HSD1 mRNA expression and enzyme activities in different tissues demonstrates that expression of the 11β-HSD1 gene is

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regulated in a species- and tissue-specific manner [13–19]. Furthermore, in the rat, hepatic 11β-HSD1 exhibits sexual dimorphism with approx. 2-fold higher levels of enzyme activity in males [18, 20]. This sex difference is associated with higher 11β-HSD1 mRNA levels in male rat liver [18].

The mouse represents a useful experimental model, particularly for development and transgenic analysis, and 11β-HSD activity has been identified in various murine tissues [21]. We have therefore isolated and determined the nucleotide sequence of a cDNA corresponding to 11β-HSD1 from the mouse, analysed its tissue-specific distribution and examined sex differences in hepatic and renal expression.

MATERIALS AND METHODS

Enzymes used in cloning were purchased from NBL Laboratories. Oligonucleotides were synthesized by Oswel DNA Service, University of Edinburgh. Radioisotopes were obtained from Amersham International, U.K. Other materials were analytical grade, and obtained from standard suppliers.

PCR-mediated cloning of mouse liver cDNA

Total RNA was prepared from the liver of a male C57BL/6 × CBA/Ca F1 mouse by the acid guanidium thiocyanate method of Chomczynski and Sacchi [22]. Single-strand cDNA synthesis was carried out using a commercial kit (Promega) and an aliquot from the reaction was used directly in PCR. Reverse transcription was carried out in a 20 μl reaction containing 5 mM $MgCl_2$, 10 mM Tris–HCl (pH 8.8), 50 mM KCl, 0.1% Triton X100, 0.5 μg oligo(dT), 1 mM dNTPs, 0.5 U RNAse inhibitor and 14 U AMV reverse transcriptase (Promega) at 42°C for 1 h. PCR reactions were carried out using oligonucleotides designed to amplify rat or human 11β-HSD1. Reactions were carried out with primer pairs 869P (5′ AAAGCTTGTCACA/TGGGGCCAGCAAA 3′, corresponding to nucleotides 178–207 of rat 11β-HSD1 cDNA) and 868P (5′ AGGATCCAG/AAGCAAACTTGCTTGCA 3′, complementary to nucleotides 648–628 of rat 11β-HSD1 cDNA) and with F206 (5′ AAAGCTTT/CTCTT/CTGTGTGTCCTACAG 3′, corresponding to nucleotides 32–52 of rat 11β-HSD1 cDNA) and 868P. 20 μl reverse transcriptase reaction was mixed with 40 pmol of each primer, and denatured at 96°C for 10 min before addition of 80 μl 1 × PCR buffer (NBL) and 2.5 U Taq DNA polymerase (NBL). 30 cycles PCR (45 s at 96°C, 30 s at 55°C, 1.5 min at 70°C) were then carried out.

3′ rapid amplification of cDNA ends (RACE) was carried out as described [23] using oligonucleotides 869P and a dT_{17}-adapter primer, 141Y (5′ GACTCGAGTCGACAT$_{17}$ 3′). Reverse transcription was carried out as described above except that adaptor primer 141Y was substituted for oligo(dT) and RNA was heated 3 min at 65°C and rapidly cooled on ice before addition of the remaining components. Following incubation at 42°C for 1 h and then 52°C for 30 min, 5 μl of the reverse transcription reaction was added to 25 pmol adaptor primer 140Y (5′ GACTCGAGTCGAC 3′) and 25 pmol 869P in a 50 μl reaction containing 10% DMSO, 1.5 mM dNTPs, and 5 μl 10 × PCR buffer (NBL). Reactions were heated at 95°C for 5 min and then held at 72°C prior to addition of 2.5 U Taq DNA polymerase, annealed at 55°C for 5 min and extended at 72°C for 40 min. Reactions were then subjected to 40 cycles of PCR (40 S at 95°C, 1 min at 55°C, 3 min at 72°C).

PCR products were purified following agarose gel electrophoresis and cloned into the vector pCR II using a commercial kit (Invitrogen). Each PCR reaction was carried out at least twice and the nucleotide sequence of at least two clones derived from independent PCR reactions were determined on both strands using the Sequenase v2.0 kit (USB).

Northern hybridization analysis of RNA

Mouse tissues were dissected on ice and kept frozen at −70°C until use. Total RNA was isolated as above and separated on a 1.2% agarose gel containing 2% formaldehyde, as previously described [18]. The RNA was transferred to Hybond-N membrane (Amersham, U.K.) and hybridized at 65°C overnight to rat 11β-HSD1 cDNA labelled with α^{32}P-dCTP using a random primed DNA labelling kit (Boehringer Mannheim GmbH). Three 15 min washes were carried out at room temperature in 1 × SSC, 0.1% SDS followed by a stringent wash at 55°C for 30 min in 0.3 × SSC, 0.1% SDS. For quantitation, duplicate autoradiographs were scanned with a Seescan Image analyser and the values normalized to 7S rRNA which provided the loading control.

Analysis of dehydrogenase activity

Male and female mouse tissues were dissected on ice and kept at 0°C, and enzyme activity assayed as previously described [18]. Briefly, homogenization of tissues was carried out in Krebs–Ringer buffer, and the protein content of the tissue homogenates determined. Concentrations of protein from each tissue was chosen so that enzyme activity was within the linear range (25 μg/ml for liver and kidney). Enzyme activity was determined by incubating tissue homogenates in buffer with 12 nM [^{3}H]corticosterone and 200 μM $NADP^+$ for 10 min. Steroids were then extracted using ethyl acetate and separated by HPLC. 11β-HSD activity was expressed as the percentage conversion to [^{3}H]11-dehydrocorticosterone. Reactions were carried out in duplicate and the sex differences analysed by unpaired Student's t-tests.

RESULTS

Isolation of the mouse liver type 11β-HSD1 cDNA

Total RNA was prepared from the liver of a male mouse and cDNA obtained by reverse transcription. The cDNA was subjected to PCR using pairs of oligonucleotide primers designed to amplify the coding regions of rat and human 11β-HSD1 cDNAs. The 3′ end of the coding region and the 3′ untranslated region was obtained by 3′ RACE. The nucleotide sequences of separate clones from at least two independent PCR reactions were determined in order to avoid including errors arising from Taq polymerase nucleotide misincorporation. The complete nucleotide sequence of mouse 11β-HSD1 cDNA is presented in Fig. 1.

Examination of the nucleotide sequence of mouse 11β-HSD1 cDNA identifies two methionines which are in the correct context for the initiation of translation, the second of which corresponds to the start of the rat protein sequence. The cDNA potentially encodes a 292 amino acid protein, with a predicted molecular weight of 32.4 kDa, with 86% identity at the amino acid level to rat 11β-HSD1, and 79% identity to human 11β-HSD1 (Fig. 2). Sequences corresponding to putative cofactor and steroid binding sites were conserved between species (Fig. 2). Two potential N-glycosylation sites were present, at residues 162–164 and 207–209, corresponding to the sites identified in the rat sequence [13] (see Fig. 2).

Primer extension analysis using an oligonucleotide complementary to mouse 11β-HSD1 mRNA was used to define the transcription start site used in the mouse liver and kidney (data not shown). The extension product obtained from RNA isolated from the mouse liver and kidney was the same length as that obtained with RNA from rat liver, indicating that the transcript probably originates at a similar position in rat and mouse. The cloning of the gene encoding mouse

```
   1 TTCTTTGTGTGTCCTACAGGGCTCCCTGAGCCAGGTCCCTGTTTGATGGCAGTTATGAAA 60
                                                   M  A  V  M  K
  61 AATTACCTCCTCCCGATCCTGGTGCTCTTCCTGGCCTACTACTACTATTCTACAAATGAA 120
      N  Y  L  L  P  I  L  V  L  F  L  A  Y  Y  Y  Y  S  T  N  E
 121  GAGTTCAGACCAGAAATGCTCCAGGGAAAGAAAGTGATTGTCACTGGGGCCAGCAAAGGG 180
      E  F  R  P  E  M  L  Q  G  K  K  V  I  V  T  G  A  S  K  G
 181  ATTGGAAGAGAAATGGCATATCATCTGTCAAAAATGGGAGCCCATGTGGTATTGACTGCC 240
      I  G  R  E  M  A  Y  H  L  S  K  M  G  A  H  V  V  L  T  A
 241  AGGTCGGAGGAAGGTCTCCAGAAGGTAGTGTCTCGCTGCCTTGAACTCGGAGCAGCCTCT 300
      R  S  E  E  G  L  Q  K  V  V  S  R  C  L  E  L  G  A  A  S
 301  GCTCACTACATTGCTGGCACTATGGAAGACATGACATTTGCGGAGCAATTTATTGTCAAG 360
      A  H  Y  I  A  G  T  M  E  D  M  T  F  A  E  Q  F  I  V  K
 361  GCGGGAAAGCTCATGGGCGGACTGGACATGCTTATTCTAAACCACATCACTCAGACCTCG 420
      A  G  K  L  M  G  G  L  D  M  L  I  L  N  H  I  T  Q  T  S
 421  CTGTCTCTCTTCCATGACGACATCCACTCTGTGCGAAGAGTCATGGAGGTCAACTTCCTC 480
      L  S  L  F  H  D  D  I  H  S  V  R  R  V  M  E  V  N  F  L
 481  AGCTACGTGGTCATGAGCACAGCCGCCTTGCCCATGCTGAAGCAGAGCAATGGCAGCATT 540
      S  Y  V  V  M  S  T  A  A  L  P  M  L  K  Q  S  N  G  S  I
 541  GCCGTCATCTCCTCCTTGGCTGGGAAAATGACCCAGCCTATGATTGCTCCCTACTCTGCA 600
      A  V  I  S  S  L  A  G  K  M  T  Q  P  M  I  A  P  Y  S  A
 601  AGCAAGTTTGCTCTGGATGGGTTCTTTTCCACCATTAGAACAGAACTCTACATAACCAAG 660
      S  K  F  A  L  D  G  F  F  S  T  I  R  T  E  L  Y  I  T  K
 661  GTCAACGTGTCCATCACTCTCTGTGTCCTTGGCCTCATAGACACAGAAACAGCTATGAAG 720
      V  N  V  S  I  T  L  C  V  L  G  L  I  D  T  E  T  A  M  K
 721  GAAATCTCTGGGATAATTAACGCCCAAGCTTCTCCCAAGGAGGAGTGCGCCCTGGAGATC 780
      E  I  S  G  I  I  N  A  Q  A  S  P  K  E  E  C  A  L  E  I
 781  ATCAAAGGCACAGCTCTACGCAAAAGCGAGGTGTACTATGACAAATCGCCTTTGACTCCA 840
      I  K  G  T  A  L  R  K  S  E  V  Y  Y  D  K  S  P  L  T  P
 841  ATCCTGCTTGGGAACCCAGGAAGGAAGATCATGGAATTTTTTTCATTACGATATTATAAT 900
      I  L  L  G  N  P  G  R  K  I  M  E  F  F  S  L  R  Y  Y  N
 901  AAGGACATGTTTGTAAGTAACTAGGAACTCCTGAGCCCTGGTGAGTGGTCTTAGAGCAGT 960
      K  D  M  F  V  S  N  *
 961  CCTGCCTGATACTTCTGTAAGCCCTACCCACAAAAGTATCTTTCCAGAGATACACAAATT 1020
1021  TTGGGGTACACCTCATCATGAGAAATTCTTGCAACACTTGCACAGTGAAAATGTAATTGT 1080
1081  AATAAATGTCACAAACCACTTTGGGGCCTGCAGTTGTGAACTTGATTGTAACTATGGATA 1140
1141  TAAACACATAGTGGTTGTATCGGCTTTACCTCACACTGAATGAAACAATGATAACTAATG 1200
1201  TAACATTAAATATAATAAAGGTAATATCAATTTTGTAAATGCAAAACTAGTAACTATGAA 1260
1261  TGGAGTTTATTTAACATGATTCCTTTAAGTCTAAACAAATG 1301
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Fig. 1. Nucleotide sequence of mouse 11β-HSD1 cDNA, with predicted amino acid sequences shown in one letter code. The putative polyadenylation sequence is underlined.

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m        1 MAVMKNYLLPILVLFLAYYYYSTNEEFRPEMLQGKKVIVTGASKGIGREM 50
r        1 ...MKKYLLPVLVLCLG.YYYSTNEEFRPEMLQGKKVIVTGASKGIGREM 46
h        1 MAFMKKYLLPILGLFMAYYYYSANEEFRPEMLQGKKVIVTGASKGIGREM 50
o        1 MAFMKKYLLPILGIFLAYYYYSANEEFRPEMLRGKRVIVTGASKGIGREM 50
s        1 MAFMKTHLLPILGLFMAYYYYSAYEEFRPEMLQGKKVIVTGASKGIGREM 50
              **  *** *      ****  ******** ** **************

m       51 AYHLSKMGAHVVLTARSEEGLQKVVSRCLELGAASAHYIAGTMEDMTFAE 100
r       47 AYHLSKMGAHVVLTARSEEGLQKVVSRCLELGAASAHYIAGTMEDMAFAE 96
h       51 AYHLAKMGAHVVVTARSKETLQKVVSHCLELGAASAHYIAGTMEDMTFAE 100
o       51 AYHLARMGAHVVVTARSEESLKKVVSRCLELGAASAHYVAGTMENMTFAE 100
s       51 AYHLAKMGAHVVVTARSKETLQKVVSHCLELGAASAHYIAGTMEDMTFAE 100
           ****  ****** **** * * **** ********** ***** * ***

m      101 QFIVKAGKLMGGLDMLILNHITQTSLSLFHDDIHSVRRVMEVNFLSYVVM 150
r       97 RFVVEAGKLLGGLDMLILNHITQTTMSLFHDDIHSVRRSMEVNFLSYVVL 146
h      101 QFVAQAGKLMGGLDMLILNHITNTSLNLFHDDIHHVRKSMEVNFLSYVVL 150
o      101 QFVAKAGELVGGLDMLILNHINYTPLRVFSNDIHLLRRSLEVNLLSYVVL 150
s      101 QFVAQAGKLMGGLDMLILNHITNTSLNFFHDDIHHVRKSMEVNFLSYVVL 150
             *   ** * **********  *    *  ***  *   *** *****

m      151 STAALPMLKQSNGSIAVISSLAGKMTQPMIAPYSASKFALDGFFSTIRTE 200
r      147 STAALPMLKQSNGSIAIISSMAGKMTQPLIASYSASKFALDGFFSTIRKE 196
h      151 TVAALPMLKQSNGSIVVVSSLAGKVAYPMVAAYSASKFALDGFFSSIRKE 200
o      151 STAALPMLKQTSGSIVVVSSVAGKIACPLAAAYSASKFALDGFFSSLRTE 200
s      151 TVAAMPMLKQSNGSIVIVSSVAGKVAYPMISAYSASKFALYGFFSSIRKE 200
             ** *****  ***   ** ***   *    ******** ****  * *

m      201 LYITKVNVSITLCVLGLIDTETAMKEISGIINAQASPKEECALEIIKGTA 250
r      197 HLMTKVNVSITLCVLGFIDTETALKETSGIILSQAAPKQECALE.IKGTV 245
h      201 YSVSRVNVSITLCVLGLIDTETAMKAVSGIVHMQAAPKEECALEIIKGGA 250
o      201 YEATKVNVSITLCILGLIDTDTEMKAVAGIYNAEASPKEECALEIIKGGA 250
s      201 YLMSEVNVSITLCVLGLIDTDTAMKAVSGIIKMNAARKEECALEIIKGGV 250
            ******** ** *** *  *   **    *  * ***** ***

m      251 LRKSEVYYDKSPLTPILLGNPGRKIMEFFSLRYYNKDMFVSN* 292
r      246 LRKDEVYYDKSSWTPLLLGNPGRRIMEFLSLRSYNRDLFVSN* 287
h      251 LRQEEVYYDSSLWTTLLIRNPCRKILEFLYSTSYNMDRFINK* 292
o      251 LRQDEVYYDNSILTSLLLKNPGRKIMEFLSLKKYNMERFINN* 292
s      251 LRQDDVYYNRSLWTTLLLRNPSRKILEFLRSTSYSTDGLIN*  291
           **   ***  *  * **  ** * * **     *
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Fig. 2. Comparisons of predicted amino acid sequences from mouse (m), rat (r), human (h), sheep (o) and squirrel monkey (s). The sequences were aligned using the Needleham–Wunsch algorithm, with manual adjustment. Sequences around the putative cofactor (residues 42–71 of the mouse sequence) and substrate (residues 166–194) binding sites are shadowed. The potential N-glycosylation sites are underlined. Identical residues in all the sequences are indicated by an asterisk.

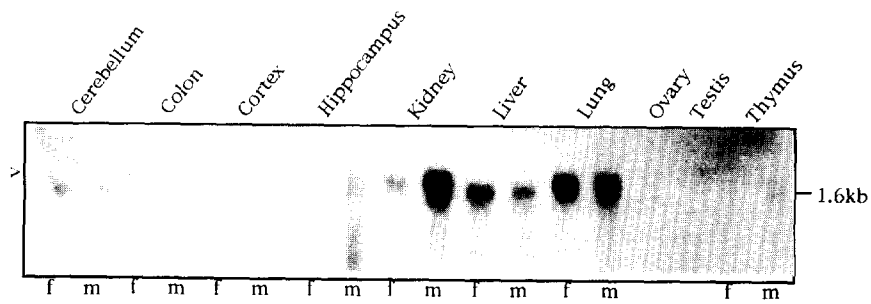

Fig. 3. Tissue distribution of mouse 11β-HSD1 mRNA. Northern blot analysis of 50 μg total RNA from all mouse tissues except liver (10 μg) probed with α^{32}P-dCTP labelled 11β-HSD1 cDNA. RNA from female tissues is on the left and from male tissues on the right. The 1.6 kb mRNA product of 11β-HSD1 is indicated. The arrowhead shows the position of 18S rRNA.

11β-HSD1 will allow the transcription initiation sequence to be identified.

Tissue specific distribution of 11β-HSD1 message

The tissue specific expression of 11β-HSD1 mRNA in mouse was examined by Northern blot analysis of total RNA from both male and female mice, separated on a denaturing agarose gel as previously described [18]. Hybridization to radiolabelled 11β-HSD1 cDNA identified a 1.6 kb species in all tissues examined, with the exception of the colon where no mRNA was detected. Abundant 11β-HSD1 mRNA was present in the liver, kidney and lung, with lower levels in the cerebellum, cortex, hippocampus, ovary, testis and thymus (Fig. 3).

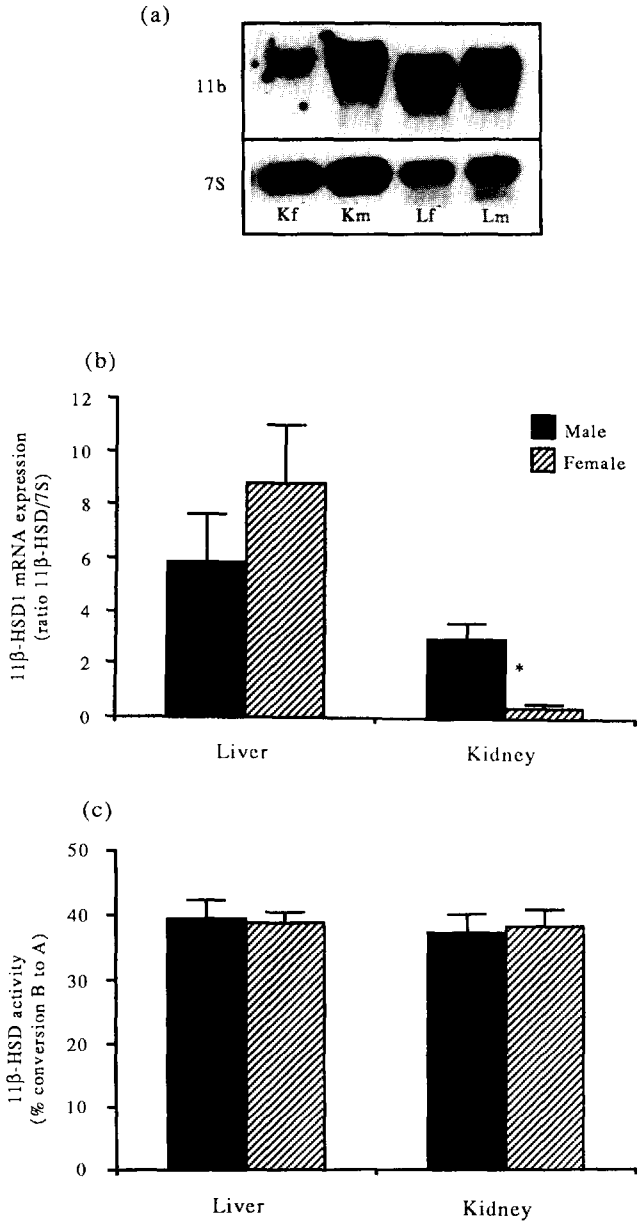

Fig. 4. 11β-HSD enzyme activity and sexual dimorphism of 11β-HSD1 mRNA in mouse kidney. (a) Representative autoradiograph of Northern blots probed with 11β-HSD1 and 7S rRNA sequences scanned to obtain relative amounts of 11β-HSD1 message in the liver (L) and kidney (K) of male (m) and female (f) mice. (b) Graphical representation in arbitrary units of 11β-HSD1 mRNA levels in mouse liver and kidney. Values are shown normalized to 7S RNA used as loading control. (c) 11β-HSD activity in tissue homogenates *in vitro*. Values are expressed as % conversion of corticosterone (B) to 11-dehydrocorticosterone (A).

Sexual dimorphism of mouse 11β-HSD1 message, but not activity in the kidney

11β-HSD1 mRNA showed dimorphism in murine kidney, with significantly higher levels in males [Figs. 3 and 4(a, b)]. The abundance of 11β-HSD1 mRNA in all other tissues, including liver and brain subregions, was similar in both sexes (Fig. 3). Analysis of 11β-HSD enzyme activity of homogenates of mouse liver and kidney demonstrated equal activities in male and female tissues [Fig. 4(c)].

DISCUSSION

We have cloned and determined the nucleotide sequence of a mouse cDNA encoding 11β-HSD1 and have analysed the tissue-specific distribution of the corresponding mRNA. Analysis of the cDNA shows extensive conservation of nucleotide (91%) and amino acid (86%) sequences with rat 11β-HSD1. The major transcription start site in the mouse is conserved between rat and mouse, indicating that the structure of the gene promotor in this region is probably also conserved. We have isolated a clone encoding part of the mouse 11β-HSD1 gene (Y. Kotelevtsev and J. J. Mullins, personal communication), and this will permit identification of regulatory regions in the mouse sequence and comparison to the rat 11β-HSD1 gene. The primary amino acid sequence is highly conserved between all the species from which 11β-HSD1 has so far been cloned (Fig. 2). This argues for a conserved functional activity of the enzyme between the species, although for 11β-HSD1, this has yet to be clearly determined.

The tissue distribution of expression of 11β-HSD1 mRNA in mouse is broadly similar to that in rat and other species. Thus, 11β-HSD1 mRNA is highly expressed in mouse liver, kidney and lung, with lower expression in brain subregions and gonads, in agreement with findings in the rat [8–10, 24], human [14], sheep [15], and squirrel monkey [16]. A notable difference was the absence of detectable expression by Northern hybridization analysis of 11β-HSD1 message in mouse colon, whereas 2 transcripts—including the predominant 1.6 kb species—have been found in rat colon [8] and at least one in human colon [14]. In the colon, aldosterone-selective mineralocorticoid activity is well described and, in addition, 11β-HSD attenuates glucocorticoid-induction of Na, K ATPase α1-subunit gene expression, actions probably mediated via glucocorticoid receptors [25]. It has been proposed that 11β-HSD1 acts as a modulator of glucocorticoid action

mediated via glucocorticoid or type II receptors, whereas 11β-HSD2 exploits a substantially higher affinity for corticosterone to exclude glucocorticoid from mineralocorticoid or type I receptors in the distal nephron [6], and possibly other mineralocorticoid target tissues. A similar or identical activity in the placenta may protect the fetus from maternal glucocorticoids [7]. Since it is likely that aldosterone-specific actions are present in mouse colon, it may be that 11β-HSD1 modulation of corticosterone effects on the glucocorticoid receptor are absent in this species, or that 11β-HSD1 mRNA is present, but at levels too low to be detected by Northern blot analysis.

Another discrepancy was the very low expression of 11β-HSD1 mRNA in mouse testis, in contrast to high expression and activity in rat and human [13, 14], but reflecting the apparently absent expression of the equivalent transcript in the squirrel monkey testis [16]. Testicular 11β-HSD has been proposed to regulate glucocorticoid inhibition of Leydig cell testosterone production at puberty [26, 27]. Leydig cells from rats show 11β-HSD1 immunoreactivity [27] and it is conceivable that the RNA from these cells was diluted in the total testis RNA preparation used in this analysis, or that alternative mechanisms are important in the mouse.

In contrast to the rat [18, 20] there is no sexual dimorphism in either hepatic 11β-HSD activity or in 11β-HSD1 mRNA levels in the mouse. The implications for sexually dimorphic hepatic functions that are sensitive to glucocorticoids in the mouse remain to be determined. In contrast, mouse kidney 11β-HSD1 mRNA shows pronounced sexual dimorphism, with higher levels in males. Interestingly, 11β-HSD activity in the mouse kidney is similar in males and females. These data parallel those in the rat kidney [18] and strongly implicate the second enzyme isoform (11β-HSD2) as responsible, at least in part, for the high 11β-HSD activity in the nephron. An alternative NAD^+-associated enzyme has been characterized in rabbit and rat kidneys [6, 7, 28] which is likely to represent the product of an unrelated gene [4, 7].

In summary, an 11β-HSD1 cDNA has been isolated from the mouse. This is similar to the rat liver-type homologue, but shows several distinct differences in tissue- and sex-specific expression. Much work has examined the teratogenic and developmental effects of glucocorticoids in the mouse. The cloning of murine 11β-HSD1 cDNA thus provides a means to study further the developmental and organ-specific functions of 11β-HSD1 in this well-characterized model.

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