Myometrial expression of 11β-hydroxysteroid dehydrogenase type 2 in rat pregnancy

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Abstract

The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which reduces glucocorticoid potency in target cells by metabolism of active glucocorticoids, is expressed in the non-pregnant rat uterus in an oestrogen-dependent manner. Because glucocorticoids appear to facilitate parturition in many species, expression of 11β-HSD2 in pregnant myometrium is likely to influence pregnancy maintenance and possibly the onset and progression of labour.

The present study therefore examined myometrial 11β-HSD2 mRNA, protein and bioactivity across rat pregnancy, with emphasis on the peripartum period. A single 1·9 kb transcript of 11β-HSD2 mRNA was evident in myometrium at all stages, with maximal ($P<0·05$) levels observed at day 16 (term = day 23). Consistent with this pattern of mRNA expression, Western blot analysis showed the presence of a 40 kDa 11β-HSD2 protein at all stages, with the maximal immunoreactive signal also observed on day 16. The 11β-HSD2 signal was immunolocalized to myometrial smooth muscle cells and endometrial stromal cells. Bioactivity specific to 11β-HSD2 was detectable in myometrium at all stages, but in contrast to the patterns of 11β-HSD2 mRNA and protein, the V_{max} decreased at the beginning of pregnancy and remained stable until term. The apparent K_m of 11β-HSD2 for corticosterone increased from 47 ± 11 nM in non-pregnant myometrium to 75 ± 7 nM by day 10 of pregnancy, and remained high until returning to an intermediate level on the day of delivery (60 ± 8 nM). Progesterone competitively inhibited 11β-HSD2 bioactivity ($K_i = 1·75$ μM) whereas 20α-hydroxypregn-4-en-3-one, the other major progestin present during rat pregnancy, had no such effect.

In conclusion, these data suggest that local levels of active glucocorticoid in the myometrium are determined by the net effects of myometrial 11β-HSD-1 and -2 expression across pregnancy. Because the previously reported increase in myometrial 11β-HSD-1 near term occurs with little change in myometrial 11β-HSD2 bioactivity, this is likely to facilitate parturition by increasing local concentrations of active glucocorticoid.

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Introduction

The uterine myometrium is a highly dynamic and adaptable tissue crucial to pregnancy maintenance and parturition, and its growth and function are influenced by a range of hormones including the female sex steroids and glucocorticoids (Challis *et al.* 2000, Whittle *et al.* 2001). Important effects of glucocorticoids on myometrial function include the inhibition of prostacyclin synthesis (Casey *et al.* 1985) and the upregulation of oestrogen receptor mRNA (Wu *et al.* 1996), both of which occur late in pregnancy and are thought to facilitate parturition. These effects are likely to be mediated via the glucocorticoid receptor (GR), access to which is dependent on local expression of the glucocorticoid-metabolizing enzymes 11β-hydroxysteroid dehydrogenase (11β-HSD) types 1 and 2. Both of these enzymes are expressed in rat uterus (Albiston *et al.* 1995, Burton *et al.* 1996, Roland & Funder 1996, Ho *et al.* 1999, Waddell & Burton 2000) in an oestrogen-dependent manner (Burton *et al.* 1998). The type 1 enzyme (11β-HSD-1) catalyses interconversion of corticosterone, the major active glucocorticoid in the rat, and the biologically inert 11-dehydrocorticosterone (11-DHC), although *in vivo* it appears to function as an 11-oxoreductase (Jamieson *et al.* 1995). In contrast, the type 2 enzyme (11β-HSD2) exclusively catalyses inactivation of corticosterone to 11-DHC (11β-dehydrogenase activity) (Albiston *et al.* 1994). Thus, the two enzymes may act in concert to either enhance or limit glucocorticoid action in the myometrium.

Recent studies show that 11β-HSD-1 is expressed in the non-pregnant rat uterus and this expression changes over the oestrous cycle (Burton *et al.* 1998), and increases after administration of gonadotrophins (Ho *et al.* 1999).

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Moreover, expression of 11β-HSD-1 increases dramatically in the uterine myometrium over the last week of pregnancy (Burton *et al.* 1996), a change that is dependent on the placenta (Waddell & Burton 2000). The non-pregnant uterus also expresses 11β-HSD2 in humans (Smith *et al.* 1997*b*) and rats (Burton *et al.* 1998, Ho *et al.* 1999), but it is not known whether this expression changes with the onset and progression of pregnancy. The continued presence of 11β-HSD2 in pregnant rat myometrium is predicted, however, by our observation that considerable 11β-dehydrogenase activity is measurable in fragments of myometrium throughout gestation (Burton *et al.* 1996), and mRNA encoding 11β-HSD2 has been localized to rat myometrium near term (Roland & Funder 1996). Potentially, changes in myometrial 11β-HSD2 could either negate or enhance the effects of the 11β-HSD-1 induction late in pregnancy, particularly since these enzymes appear to favour opposite catalytic activities *in vivo*. Therefore, the present study examined the patterns of 11β-HSD2 mRNA, protein and bioactivity in the myometrium at various stages of rat pregnancy, with emphasis on the peripartum period. The relative inhibitory effects of progesterone and 20α-hydroxypregn-4-en-3-one (20α-OHP) on 11β-HSD2 bioactivity were also examined, since a dramatic reversal in the relative concentrations of these progestins occurs over the final days of rat pregnancy (Waddell *et al.* 1989). Although several progestins, including progesterone, can potently inhibit 11β-HSD activity (Lopez-Bernal *et al.* 1980, Baggia *et al.* 1990, Souness & Morris 1996), it is not known whether 20α-OHP exerts a similar inhibitory effect on 11β-HSD2.

Materials and Methods

Animals and chemicals

Nulliparous albino Wistar rats, 3–5 months old and weighing 269 ± 34 g (means ± S.D.) at mating were obtained from the Animal Resources Centre (Murdoch, WA, Australia). Rats were mated overnight and the morning on which spermatozoa were present in a vaginal smear was designated day 1 of pregnancy. All procedures involving animals were conducted only after approval by the Animal Ethics Committee of the University of Western Australia.

A Vectastain *Elite* ABC kit was purchased from Vector Laboratories (Burlingame, CA, USA). Corticosterone, biotinylated molecular weight standards and nitrocellulose membranes were obtained from Sigma Chemical Co. (St Louis, MO, USA). TLC plates precoated with silica gel 60 F_{254} were obtained from Merck (Darmstadt, Germany), and [1,2,6,7-^{3}H]corticosterone and [α-^{32}P]deoxy-CTP were purchased from Amersham Australia (Sydney, Australia).

Tissue preparation

Tissues for Northern and Western blots were obtained from rats anaesthetized with halothane/nitrous oxide on the day of post-oestrus of the cycle, on days 5, 10, 16, 22 and 23 of pregnancy, and 24 h postpartum. Tissues were also obtained for 11β-HSD2 bioassays on each of these days except day 5 of pregnancy. Both uterine horns were removed immediately and myometrial tissue was isolated and collected as previously described (Burton *et al.* 1996), snap frozen on liquid nitrogen and stored at − 80 °C for subsequent Northern and Western blot analyses or placed into ice-cold phosphate-buffered saline (PBS; pH 7·4) containing 0·25 M sucrose and homogenized for 11β-HSD2 bioassays. Uterine tissue was also obtained for immunolocalization of 11β-HSD2 on days 16 and 22 of pregnancy and 1 day postpartum. These tissues were immersion fixed and then processed as previously described (Burton *et al.* 1996).

Northern blot analysis

Northern blot analysis (n=3 per group) was performed as previously described (Burton *et al.* 1996). Briefly, total RNA was extracted using the single step guanidinium thiocynanate method (Chomczynski & Sacchi 1987) and 30 μg were fractionated by electrophoresis on 1% agarose–17% formaldehyde gels, transferred to nylon membranes (MagnaGraph from MSI, Westboro, MA, USA) by capillary blotting and fixed by UV crosslinking (UV Crosslinker RPN 2500; Amersham International plc, Aylesbury, Bucks, UK). Membranes were prehybridized (0·2 M NaH_2PO_4, 0·6 M $NaHPO_4$, 5 mM EDTA, 200 μg denatured herring testis DNA and 20% SDS) for 4 h at 55 °C and then hybridized overnight (55 °C) in identical buffer containing an 11β-HSD2 cDNA probe (Albiston *et al.* 1994). The probe was labelled with [α-^{32}P]deoxy-CTP using a Random Primed DNA Labelling Kit (Boehringer Mannheim, Mannheim, Germany) and diluted to 2–3 × 10^{6} c.p.m./ml. Membranes were washed to a final stringency of 0·3 × SSC–0·1% SDS at 55 °C and exposed to Kodak XAR film (Eastman Kodak, Rochester, NY, USA) for 3 days. To confirm even loading of RNA, membranes were stripped and rehybridized under identical conditions with a [α-^{32}P]deoxy-CTP labelled 18S probe. To quantify the 11β-HSD2 and 18S signals, hybridzed membranes were exposed to a Fuji Imaging Plate (Bas-IIIs; Fuji Photo Film Co., Tokyo, Japan), and the resultant images scanned using a Fuji Bioimager as previously described (Burton *et al.* 1996).

Western blot analysis

Western blot analysis (n=3 per group) of 11β-HSD2 was performed as previously described (Burton *et al.* 1998)

using an antibody (RAH23, a kind gift of Dr Z Krozowski, Baker Medical Research Institute, Melbourne, Australia) raised against a portion of rat 11β-HSD2 (Smith *et al.* 1997*a*). Briefly, myometrial tissue was homogenized in 4 vol. 10 mm sodium phosphate buffer (pH 7·0) containing 0·25 M sucrose, 1 μM EDTA, 1 μM phenylmethylsulphonylfluoride and 100 μg/ml trypsin inhibitor. Microsomes were recovered by sequential centrifugation, subjected to Western blot analysis and 11β-HSD2 signal visualized using a Vectastain *Elite* ABC kit. To quantify this signal, blots were incubated with a ^{125}I-labelled anti-rabbit IgG secondary antibody (Amersham, Sydney, Australia), exposed on a Fuji Imaging Plate and the resultant images scanned and quantitated by densitometry using a Fuji Bioimager.

Immunolocalization of 11β-HSD2

Immunolocalization of 11β-HSD2 was carried out as previously described for non-pregnant rat uterus (Burton *et al.* 1998). Briefly, after sectioning, paraffin was removed and non-specific staining blocked by incubation of tissue sections (4 μm) with 3% hydrogen peroxide in methanol for 10 min, followed by incubation with 2% bovine serum albumin–PBS–0·02% Triton X-100 for 20 min. Tissue sections were then exposed to immunopurified 11β-HSD2 antibody (see details in section on Western analyses) at a final concentration of 0·5 μg/ml. Positive immunostaining was identified by the addition of an anti-rabbit IgG biotinylated secondary antibody followed by avidin–biotin–peroxidase complex (Vectastain *Elite* ABC kit) and diaminobenzidine. Sections were counterstained with Gill's haematoxylin.

11β-HSD2 bioassay

Myometrial 11β-HSD2 bioactivity was measured by the method previously described for rat corpus luteum (Waddell *et al.* 1996). Briefly, myometrial and kidney homogenates (125–500 μg/ml supernatant protein; Bio-Rad protein assay kit; Bio-Rad, Hemel Hempstead, Herts, UK) were incubated with [^{3}H]corticosterone (15 nM), 400 nM NAD^+ and varying concentrations of authentic corticosterone (range 0–515 nM). Preliminary studies established that linearity of conversion was maintained beyond the 10-min incubation at the protein concentration used. Duplicate incubations were carried out in a shaking water bath at 37 °C for 10 min in a total volume of 0·25 ml. Incubations were stopped by the addition of 2·5 ml ethyl acetate, into which steroids were extracted and isolated by thin-layer chromatography (chloroform:ethanol, 96:4). [^{3}H]Corticosterone and [^{3}H]11-DHC were quantified using liquid scintillation spectrometry. The reaction velocities (pmol 11-DHC formed/min per mg protein) for each incubation set were used to construct Lineweaver–Burk plots, from which the

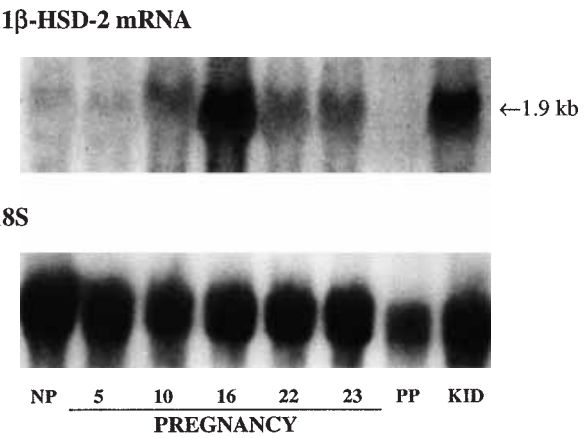

Figure 1 Northern blot analysis of total RNA from myometrium. The upper panel shows mRNA for 11β-HSD2 and the lower panel 18S before (NP), at different days throughout (5, 10, 16, 22, 23) and 24 h after (PP) pregnancy. Maternal kidney (KID) was included as a positive control. Blots were probed with a ^{32}P-labelled 11β-HSD2 cDNA, then stripped and reprobed with ^{32}P-labelled 18S cDNA to confirm RNA loading.

Michaelis–Menten constant (K_m) and maximum velocity (V_{max}) values were derived (Palmer 1995). To assess inhibition of 11β-HSD2 bioactivity by progesterone and 20α-OHP, similar incubations were conducted with [^{3}H]corticosterone (15 nM) and authentic corticosterone (100, 200 and 500 nM) in the presence of varying concentrations of these progestins (0·5, 1·0 and 2·0 μM), and the inhibitor constant (K_i) derived from a Dixon plot (Palmer 1995).

Statistical analysis

Changes in 11-HSD2 mRNA and immunoreactivity were assessed using two-way ANOVA and least significant difference (LSD) tests (Snedecor & Cochran 1989), with each Northern or Western blot respectively containing a sample from each stage of pregnancy. Thus, within each two-way ANOVA, individual blots served as replicates ($n=3$) and stages of pregnancy as treatments ($n=7$). Changes in 11-HSD2 bioactivity with gestational age and the inhibitory effects of progesterone and 20α-OHP at day 16 were assessed by one-way ANOVA and LSD tests (Snedecor & Cochran 1989). Lineweaver–Burk and Dixon plots were determined by the method of least squares and the K_i derived from the Dixon plot by visual inspection.

Results

11β-HSD2 mRNA and protein expression

A single 1·9 kb transcript of 11β-HSD2 mRNA was evident from Northern blot analysis of myometrium at all

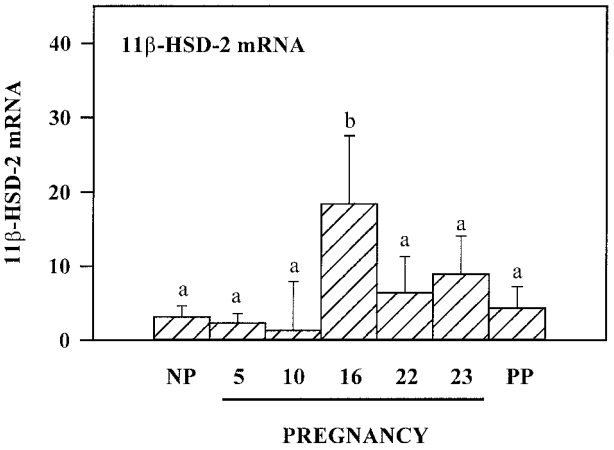

Figure 2 Quantitation of myometrial 11β-HSD2 mRNA expression (arbitrary units) measured by Northern blot analysis before (NP), at different days throughout (5, 10, 16, 22, 23) and 24 h after (PP) pregnancy. Northern blots were exposed onto a phosphor imaging plate and the resultant images quantified with a Fuji Bioimager. Values are the means ± S.E.M. (n=3 per group), and those without common letter superscripts differ significantly (P<0·05, two-way ANOVA and LSD tests).

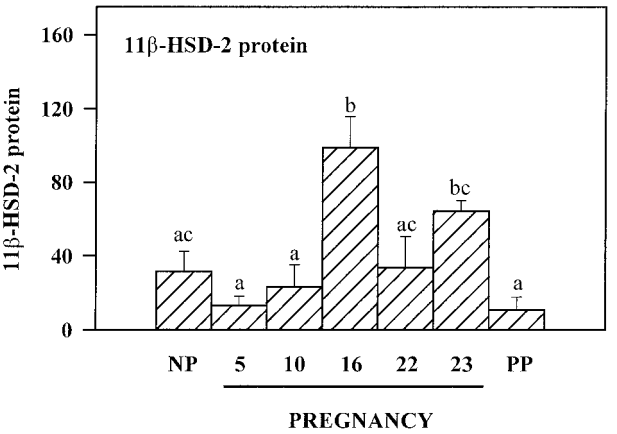

Figure 4 Quantitation of 11β-HSD2 immunoreactivity (arbitrary units) measured by Western blot analysis of myometrium before (NP), at different days throughout (5, 10, 16, 22, 23) and 24 h after (PP) pregnancy. After incubation with 11β-HSD2 antiserum, blots were incubated with a ^{125}I-labelled anti-rabbit IgG secondary antibody and exposed onto a phosphor imaging plate and the resultant images quantified with a Fuji Bioimager. Values are the means ± S.E.M. (n=3 per group), and those without common letter superscripts differ significantly (P<0·05, two-way ANOVA and LSD tests).

stages examined, and corresponded with that in a kidney positive control (Fig. 1). Quantification of this mRNA signal showed that levels varied significantly over gestation (P<0·05; two-way ANOVA), being higher at day 16 compared with all other stages (P<0·05, LSD test; Fig. 2). Consistent with this pattern of 11β-HSD2 mRNA expression, Western blot analysis of myometrium demonstrated the presence of a 40 kDa 11β-HSD2 protein (comparable to that in kidney positive control) at all stages examined (Fig. 3). Quantitative analysis showed that this 11β-HSD2 immunoreactive signal also varied significantly across pregnancy (P<0·05, two-way ANOVA), with maximal levels evident on days 16 and 23 (P<0·05, LSD test; Fig. 4). This immunoreactive signal was localized specifically to myometrial cells at all stages of pregnancy examined and, consistent with the Western blot data, the intensity of immunostaining appeared considerably lower 1 day postpartum (Fig. 5a and c). Prominent staining for 11β-HSD2 was also evident in stromal cells immediately adjacent to the reformed uterine luminal epithelium, but epithelial cells were clearly immunonegative (Fig. 5d).

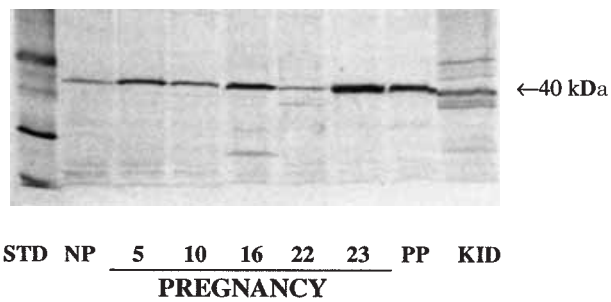

Figure 3 Western blot analysis of 11β-HSD2 protein in microsomal fractions of myometrium before (NP), at different days throughout (5, 10, 16, 22, 23) and 24 h after (PP) pregnancy. Biotinylated molecular weight standards (STD) were used to estimate the molecular weight of immunostained proteins and maternal kidney (KID) was used as a positive control.

11β-HSD2 bioactivity

Bioactivity specific to 11β-HSD2 was detectable in myometrium at all stages examined (K_m in the range of 40–80 nM; Table 1), and V_{max} (indicative of enzyme concentration) varied significantly with stage of gestation (P<0·01, one-way ANOVA; Table 1). Unlike the pattern for 11β-HSD2 mRNA and protein, however, myometrial 11β-HSD2 bioactivity was maximal before pregnancy and on the day of delivery (day 23), but there was no peak evident at day 16. The apparent K_m also changed with the onset of pregnancy (P<0·05, one-way ANOVA), increasing substantially from 47 ± 11 nM in non-pregnant myometrium to 75 ± 7 nM by day 10, and remained elevated until returning to an intermediate level on the day of delivery (60 ± 8 nM).

Inhibition of 11β-HSD2 bioactivity by progesterone and 20α-OHP

Because high concentrations of either progesterone or 20α-OHP are present for most of rat pregnancy, their possible inhibitory effects on myometrial 11β-HSD2 bioactivity were examined. Progesterone clearly inhibited

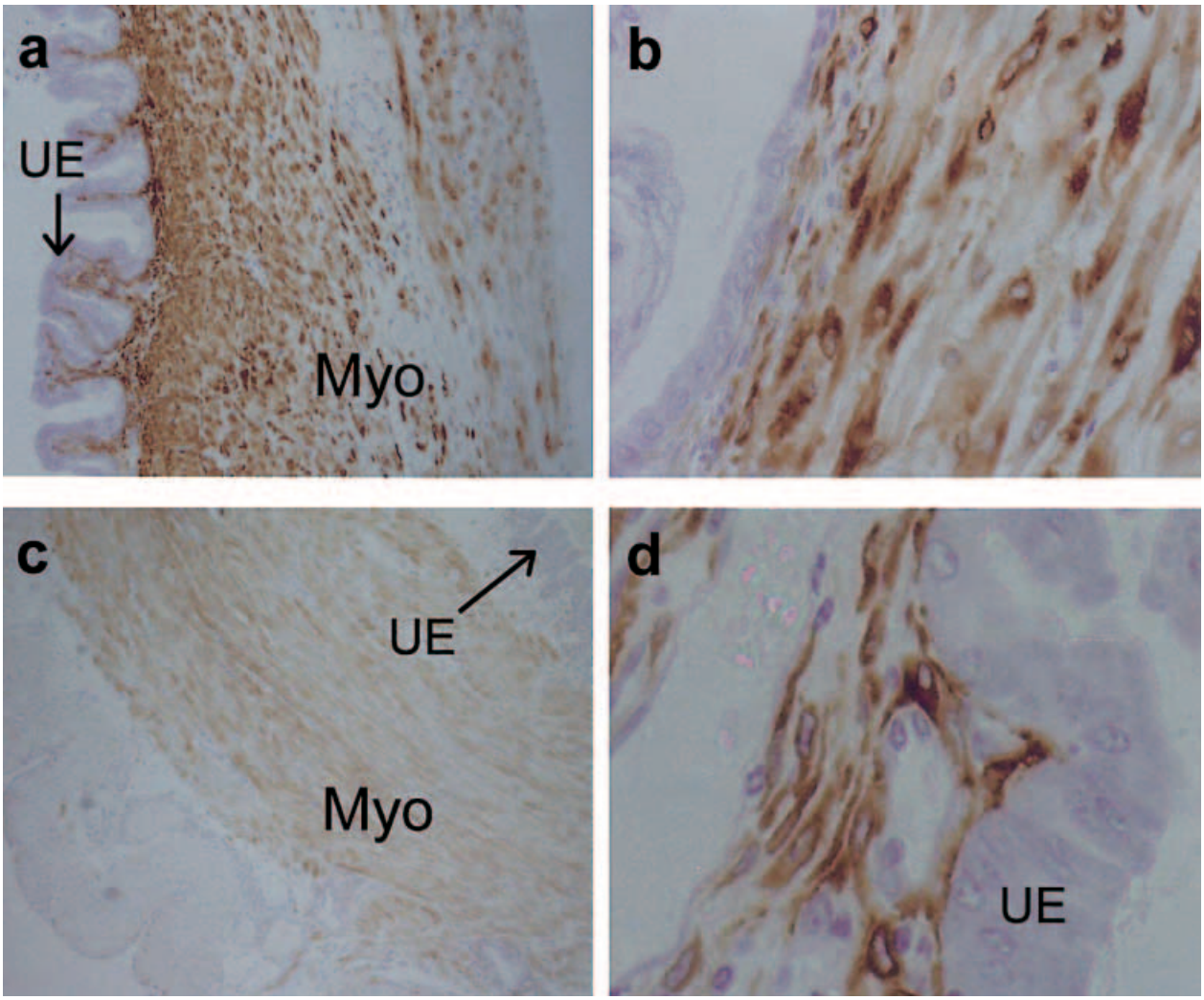

Figure 5 Immunolocalization of 11β-HSD2 in the rat uterus at days 16 and 22 of pregnancy and 1 day postpartum. (a) Day 16 of pregnancy; note positive immunoreactivity in the myometrium (Myo) and in stromal cells below uterine epithelium (UE). (b) Myometrial cells at day 22 (high-power view); note immunostaining for 11β-HSD2 in individual smooth muscle cells. (c) Day 1 postpartum; note reduced intensity of immunostaining in myometrium relative to day 16. (d) 11β-HSD2 immunostaining of endometrial stromal cells on day 22 (high-power view); note absence of immunostaining in the overlying uterine epithelium.

11β-HSD2 bioactivity at all concentrations tested (0·5–2·0 μM, $P<0·01$, Fig. 6), and the resultant Dixon plot is shown in Fig. 7. The derived K_i for progesterone was 1·75 μM. In contrast, 20α-OHP had no effect on 11β-HSD2 bioactivity over the same concentration range (Fig. 6).

Table 1 V_{max} (pmol/min per mg protein) and K_m (nM) for 11β-HSD-2 bioactivity in myometrium obtained prior to (at post-oestrus (NP)), during (days 10, 16, 22 and 23) and after (24-h postpartum, PP) pregnancy. Values are the mean ± S.E.M. ($n=4$ per group)

	NP	Day 10	Day 16	Day 22	Day 23	PP	*P**
V_{max}	$3·9 \pm 0·5^{a}$	$2·0 \pm 0·4^{b}$	$2·4 \pm 0·3^{bc}$	$2·4 \pm 0·1^{bc}$	$2·6 \pm 0·1^{bc}$	$3·2 \pm 0·1^{ac}$	<0·01
K_m	47 ± 11^{a}	75 ± 7^{b}	79 ± 5^{b}	78 ± 6^{b}	60 ± 8^{ab}	63 ± 7^{ab}	<0·05

**P* value derived from one-way ANOVA; values without common superscripts differ significantly ($P<0·05$, LSD test).

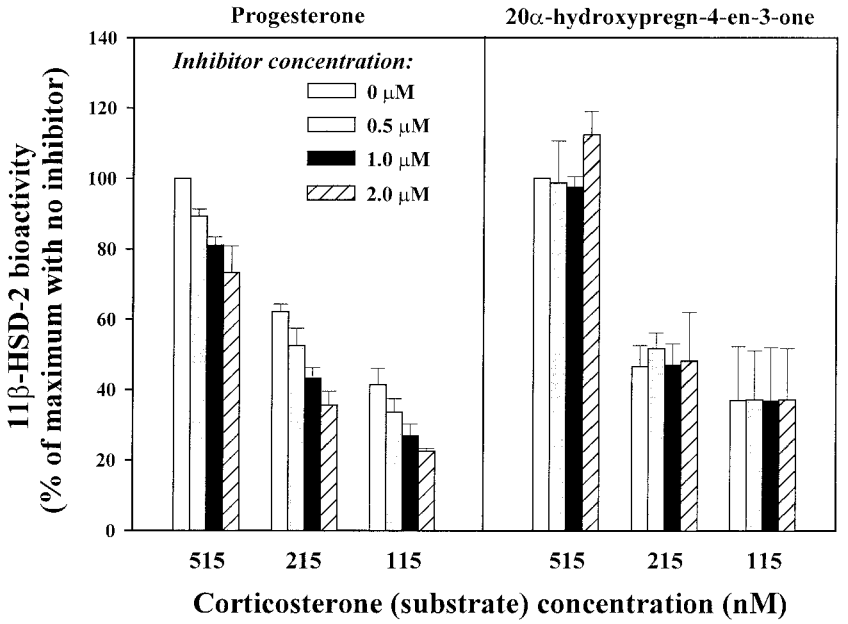

Figure 6 Inhibition of 11β-HSD2 bioactivity in homogenates of day-16 myometrium by progesterone and 20α-OHP. Myometrial homogenates (500 μg/ml protein) were incubated with [^{3}H]corticosterone (15 nM), authentic corticosterone (100, 200 and 500 nM) and NAD^+ (400 nM) in the presence of varying concentrations of either progesterone or 20α-OHP (0·5, 1·0 and 2·0 μM). Values shown are the reaction velocities expressed as a percentage of that measured in the presence of maximum substrate (515 nM) and no inhibitor, and are the means ± S.E.M. (n=3–4 per group). 11β-HSD2 activity was inhibited at each concentration of progesterone (P<0·01, P<0·001 and P<0·05 for substrate concentrations of 115, 215 and 515 nM respectively; two-way ANOVAs) but not 20α-OHP.

Discussion

Glucocorticoids exert a range of important effects on the uterine myometrium, particularly in the peripartum period (Challis *et al.* 2000, Whittle *et al.* 2001) when maternal and fetal plasma concentrations of corticosterone are maximal (Dupouy *et al.* 1987, Atkinson & Waddell 1995). As in many other glucocorticoid target tissues, activation of the GR in myometrium is determined not only by blood concentrations of active glucocorticoid, but also by local expression of the 11β-HSD enzymes. We have previously demonstrated that 11β-HSD-1 and -2 are both expressed in an oestrogen-dependent manner in the myometrium of the non-pregnant rat (Burton *et al.* 1998), and during pregnancy 11β-HSD-1 mRNA, protein and associated bioactivity increase dramatically near term (Burton *et al.* 1996, Waddell & Burton 2000). The present study shows that 11β-HSD2 mRNA, protein and bioactivity are also present in rat myometrium before, during and after pregnancy, with mRNA and protein peaking at day 16. Moreover, 11β-HSD2 was immunolocalized to myometrial smooth muscle cells, the same localization as that for 11β-HSD-1 and the GR (Burton *et al.* 1996). Colocalization of the two 11β-HSD enzymes within myometrial cells is similar to observations in the placenta of several species where both enzymes are expressed in trophoblast cells (for review see Burton & Waddell 1999). The physiological consequences of myometrial colocalization are uncertain, however, since each enzyme is thought to favour catalysis of opposite reactions *in vivo*. Thus, 11β-HSD2 exclusively catalyses 11β-dehydrogenase activity (glucocorticoid inactivation) (Albiston *et al.* 1994), whereas 11β-HSD-1 primarily exhibits 11-oxoreductase activity (Jamieson *et al.* 1995). Therefore, the net physiological effect of 11β-HSD-1 and -2 colocalization in myometrium is likely to depend on their relative expression levels and possibly local cofactor availability. We suggest that the more than 30-fold increase of myometrial 11β-HSD-1 expression and associated 11-oxoreductase activity near term (Burton *et al.* 1996) should over-ride the relatively stable 11β-dehydrogenase activity attributable to myometrial 11β-HSD2. This shift towards 11-oxoreductase dominance should increase local levels of active glucocorticoid within the myometrium and thereby enhance activation of the GR. The effects of glucocorticoids on several indices of myometrial function (Whittle *et al.* 2001) suggest that this increased GR activation would facilitate parturition.

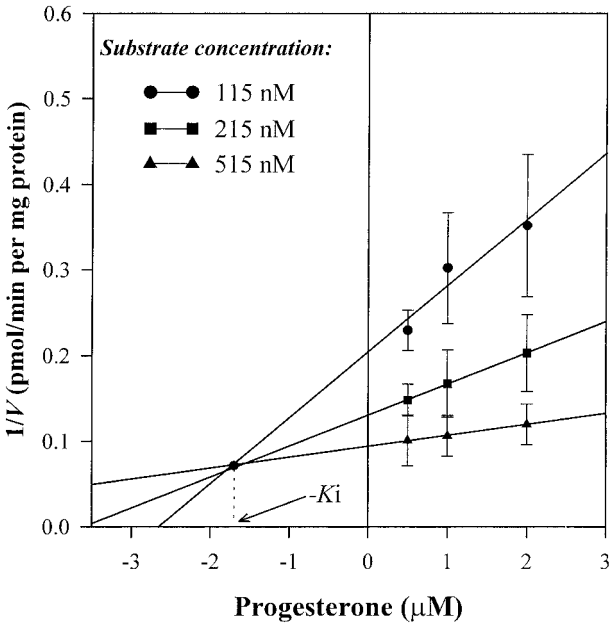

Figure 7 Dixon plot for progesterone inhibition of 11β-HSD2 bioactivity in homogenates of day-16 myometrium. Myometrial homogenates (500 μg/ml protein) were incubated with [^{3}H]corticosterone (15 nM), authentic corticosterone (100, 200 and 500 nM) and NAD^+ (400 nM) in the presence of varying concentrations of progesterone (0·5, 1·0 and 2·0 μM). Each line shows the reciprocal of the reaction velocities plotted against progesterone concentration, and the K_i was derived as the progesterone concentration at which the three resultant plots intercept (1·75 μM). Values are the means ± S.E.M. (n=3–4 per group).

The apparent K_m for myometrial 11β-HSD bioactivity was in the range of 40–80 nM, consistent with previously reported values for 11β-HSD2-specific bioactivity (Albiston *et al.* 1994, Waddell *et al.* 1998). The fall in enzyme concentration (i.e. V_{max}) during pregnancy, however, was not paralleled by changes in either mRNA or protein expression, possibly reflecting a contribution of 11β-HSD-1 in the bioassay. Although the substrate concentrations (15–215 nM) and cofactor (NAD^+) used in the bioassay should limit such a contribution, it remains a possibility given the very high expression levels of 11β-HSD-1 in myometrium near term (Burton *et al.* 1996).

Progesterone, but not 20α-OHP, clearly inhibited myometrial 11β-HSD2 in a competitive manner. The relatively high K_i of this inhibition (1·75 μM), however, together with the relative concentrations of corticosterone and progesterone, suggest that this inhibition may be of minimal physiological importance. Plasma concentrations of corticosterone peak at around 1 μM during late pregnancy (Atkinson & Waddell 1995), whereas progesterone concentrations fall from a maximum of 0·25 μM at day 16 to only 0·05 μM at day 22 (Waddell *et al.* 1989). In contrast, progesterone inhibition of 11β-HSD2 in both human (Lopez-Bernal *et al.* 1980) and baboon (Baggia *et al.* 1990) placenta is likely to be physiologically relevant since the placenta of these species is a source of progesterone. Thus, local placental concentrations of progesterone are likely to be considerably higher than the K_i measured for inhibition of 11β-HSD2 in this tissue (0·2 μM; Baggia *et al.* 1990).

In conclusion, this study demonstrates that 11β-HSD2 is expressed in the rat myometrium throughout pregnancy, and is likely to interact with myometrial 11β-HSD-1 to determine local concentrations of active glucocorticoid. Because of the facilitative role played by glucocorticoids in uterine contraction, the relative expression patterns of the two 11β-HSD enzymes in myometrium near term (i.e. rising 11β-HSD-1/stable 11β-HSD2), are likely to make an important contribution to the complex hormonal control of parturition.

Acknowledgements

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