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Minireview

Dual Function of 11β-Hydroxysteroid Dehydrogenase in Placenta: Modulating Placental Glucocorticoid Passage and Local Steroid Action[1]

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ABSTRACT

Target cell metabolism of glucocorticoids is now recognized as an important modulator of ligand access to the glucocorticoid receptor (GR). This metabolism occurs via two distinct 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes (types 1 and 2) that catalyze interconversion of active glucocorticoids (cortisol and corticosterone) and their inactive 11-keto products (cortisone and 11-dehydrocorticosterone, respectively). The focus of this review is on the biology of the 11β-HSD enzymes in the placenta, where they also regulate passage of maternal glucocorticoids to the fetus. The presence of this metabolic barrier at the maternal-fetal interface is potentially crucial to fetal growth and development, since maternal glucocorticoid levels are elevated in pregnancy and since excess glucocorticoid exposure in fetal life has detrimental effects on prenatal growth and increases susceptibility to disease in subsequent adult life. In primates, transplacental glucocorticoid passage also appears to play an important role in the induction of an autonomous fetal hypothalamic-pituitary-adrenal axis near term. Placental 11β-HSD is also likely to modulate glucocorticoid actions within the placenta, per se, by regulating their access to placental GR. Moreover, because some progesterone effects are exerted via the GR, placental 11β-HSD may regulate progesterone-glucocorticoid competition for access to this receptor and thereby affect the biological actions of both steroids in the placenta.

INTRODUCTION

Adrenal glucocorticoid hormones exert potent effects on cellular function in essentially all organ systems, particularly in terms of differentiation and homeostasis. These actions are of particular importance in mammalian pregnancy, with glucocorticoids known to influence metabolic adaptation in the mother [1, 2], maturation of fetal organ systems [3], and the timing of parturition [4]. Associated with these roles are marked and sustained changes in the maternal hypothalamic-pituitary-adrenal (HPA) axis with advancing gestation, with a rise in plasma glucocorticoids characteristic of late pregnancy in a range of different species [1, 2, 5].

While maternal glucocorticoids presumably serve to mobilize energy stores for the rapidly growing fetus near term [2], they can also have profound effects on fetal growth [6] and development [3] if they cross the placenta to reach the fetal circulation. It is now well established that transplacental passage of glucocorticoids is regulated within the placenta by 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes [7] that interconvert active and inactive glucocorticoids. Because glucocorticoids provide key signals in cellular differentiation, many of their effects are long-lasting, and excess glucocorticoid exposure in utero has been directly linked to the subsequent development of disease in adult life [8] (see below).

The placenta is also a glucocorticoid target organ per se, with placental growth [6, 9] and endocrine function [10] known to be affected by glucocorticoids. Glucocorticoid-binding activity [11, 12] and mRNA encoding the glucocorticoid receptor [13] are readily demonstrable in placental tissue. Clearly, therefore, the placenta is a central player in the biology of glucocorticoids in pregnancy, not only because of its location at the maternal-fetal interface, but also as a reflection of its central role in hormone-dependent adaptations in the mother. This review details the roles of the placental 11β-HSD enzymes in determining passage of maternal glucocorticoids to the fetus and modulating local glucocorticoid actions within the placenta.

Glucocorticoid Hormone Action and 11β-HSD

Glucocorticoids exert their biological action via interaction with at least two distinct receptors (types I and II, or mineralocorticoid receptor and glucocorticoid receptor [GR], respectively) in target cells, with the clear majority of effects occurring via GR (for review see [14]). Extensive work over the last decade has established that access of glucocorticoid hormones to their receptors within target cells is regulated by the local expression of the enzyme 11β-HSD (for reviews see [15, 16]). Two distinct gene products that exhibit 11β-HSD activity are now recognized. The type 1 form (11β-HSD-1) is $NADP^+$/H-preferring with a K_m in the micromolar range for corticosterone and cortisol; it was originally purified [17] and the cDNA cloned [18] from rat liver. Although 11β-HSD-1 can catalyze the interconversion of active cortisol with the biologically inert cortisone (or corticosterone and 11-dehydrocorticosterone in rodents), this form of the enzyme appears to act primarily as an 11-oxoreductase in vivo (i.e., formation of cortisol and corticosterone from their 11-keto forms) [19–21]. Accordingly, 11β-HSD-1 messenger RNA expression is highly correlated with 11-oxoreductase activity in rat myometrium [22] and placenta (see below). The 11β-HSD-1 enzyme is widely distributed in glucocorticoid target tissues

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including the liver [23], brain [24, 25], uterus [22, 26–28], and ovary [29].

In contrast to 11β-HSD-1, the type 2 form (11β-HSD-2) is NAD^+ dependent, has a K_m in the nanomolar range for corticosterone and cortisol, and catalyses their conversion to 11-dehydrocorticosterone and cortisone, essentially unidirectionally [30–33]. The 11β-HSD-2 cDNA was initially cloned from kidney in several species [30–34], and subsequently the protein was purified from human placenta by Brown et al. [35]. 11β-HSD-2 is expressed primarily in mineralocorticoid target tissues [36–38], the female reproductive tract [22, 28, 39], the corpus luteum of the ovary [40], and the placenta (see below).

Placental 11β-HSD Bioactivity

Studies in the 1950s first established that high levels of cortisone could be isolated from human placenta [41, 42], with Osinski [43] subsequently demonstrating the presence of 11β-HSD bioactivity in homogenates of term human placenta and chorion. A decade later, Pasqualini et al. [44] showed that the midgestation human placenta was capable of interconverting radiolabeled cortisol and cortisone in vivo. It was subsequently shown that up to 85% of cortisol injected into the maternal circulation eventually reached the umbilical circulation as cortisone [45]. These early data showing substantial 11β-HSD bioactivity in the placenta have since been confirmed by extensive research in the human [35, 46–51] and in several other species including the baboon [47, 52–55], sheep [56, 57], rat [9, 48, 58–60], and pig [61].

From a functional standpoint, placental 11β-HSD is generally assumed to provide a glucocorticoid barrier at the maternal-fetal interface by inactivating maternal cortisol and corticosterone (via 11β-dehydrogenase activity) [7], but the reverse 11-oxoreductase activity may also be important physiologically. Measurement of this enzyme activity in vitro, however, has proven difficult because of its relative instability following cell disruption. Thus, Burton and Waddell [9] demonstrated that while tissue fragments of rat placenta efficiently convert 11-dehydrocorticosterone to corticosterone, this 11-oxoreductase activity was almost completely abolished by homogenization. Similarly, Lakshmi et al. [50] showed that although 11-oxoreductase activity was measurable in subcellular fractions of human placenta under conditions of low pH, this activity was very labile.

11β-HSD-1 and -2 Gene Expression

On the basis of cofactor preference, 11β-HSD-2 appears to be the major form expressed in the placenta [48], consistent with its recent purification from human placenta [35] and expression of its mRNA and protein in human [35, 49, 51, 62–65], baboon [54, 55], and rat [37, 39, 60] placenta. Expression of 11β-HSD-2 has been specifically localized to the syncytiotrophoblast by in situ hybridization in the rat [13, 39] and by immunocytochemistry in the human placenta [62, 63]. Despite this clear evidence for 11β-HSD-2 expression in the placenta, 11β-HSD bioactivity is still readily apparent in the rat [9, 48], human [50], and pig [61] placenta with $NADP^+$ as cofactor, and placental tissue fragments exhibit substantial 11-oxoreductase activity [9, 54, 60]. Both of these observations suggest that the placenta may also express 11β-HSD-1, and mRNA for 11β-HSD-1 has been observed in the placenta of the sheep [56, 57], baboon [54, 55], and rat [60]. In contrast, Stewart et al. [51, 64] did not detect 11β-HSD-1 expression in human placental villous tissue, consistent with the recent observation of Sun et al. [63] that 11β-HSD-1 immunoreactivity was not detectable in syncytiotrophoblast but was present in human extravillous trophoblast, fetal membranes, and endothelial cells. In other species, however, mRNA encoding 11β-HSD-1 has been specifically localized to the syncytiotrophoblast (baboon [55]; rat [13]), and it is also noteworthy that there are marked differences in 11β-HSD-1 (and 11β-HSD-2) expression between the two major zones of the rat placenta [13, 60] (see below).

It is clear, therefore, that while the placenta expresses both forms of 11β-HSD, the relative expression of each varies considerably among species and even within the placenta of a given species. How the two enzymes interact in a physiological setting is less clear, but a major determinant of this interaction will be the apparent Michaelis constant (K_m) of each 11β-HSD enzyme. Given the nanomolar K_m levels for 11β-HSD-2, this form is more likely to play an important physiological role. Notably, however, despite its high K_m (in the micromolar range), 11β-HSD-1 may act as a physiological 11β-dehydrogenase in the placenta [7] as it does in the rat testis [66].

Gestational Changes in Placental 11β-HSD

Given the crucial role played by glucocorticoids in fetal growth and development, gestational changes in placental 11β-HSD expression and associated bioactivity could provide key regulatory signals by altering fetal exposure to maternal glucocorticoids. Changes in placental 11β-HSD bioactivity with advancing pregnancy were first noted by Giannopoulos et al. [67], who showed that the relative amount of 11-oxoreductase activity increased toward term in fragments of placental tissue, although 11β-dehydrogenase activity always predominated. As discussed above, however, the favored direction of 11β-HSD activity in vitro is greatly influenced by enzyme stability as well as assay conditions (substrate supply, pH, etc.), and so the relevance to placental physiology remains uncertain. On the other hand, indirect estimates of placental 11β-HSD activity in vivo (by the constant isotope infusion approach) have demonstrated a shift from 11-oxoreductase to 11β-dehydrogenase dominance between mid and late gestation in the baboon, implying an increase in the placental glucocorticoid barrier over this period [68] (see Fig. 1). Consistent with this observation, mRNA for both 11β-HSD-1 and -2 increases in the baboon placenta with advancing pregnancy [55], although the relative contribution of these two enzymes to placental glucocorticoid metabolism in vivo remains uncertain.

Marked changes in placental 11β-HSD bioactivity have also been observed with advancing gestation in other species, but no consistent pattern in the nature of this change is evident. Thus, while 11β-dehydrogenase bioactivity decreases with advancing pregnancy in sheep placenta [7], it increases toward the end of gestation in the rat (whole placenta) [9] and pig [61]. While these inconsistencies may reflect important species differences in the function of 11β-HSD, recent work in the rat suggests that they could relate at least in part to regional differences in 11β-HSD expression within placental tissue. Thus, although 11β-dehydrogenase activity clearly increased toward term in fragments of whole placenta [9], separate analysis of the two morphologically and functionally distinct placental zones (basal and labyrinth) showed opposite patterns of change [60]. Specifically, while net 11β-dehydrogenase bioactivity (11β-

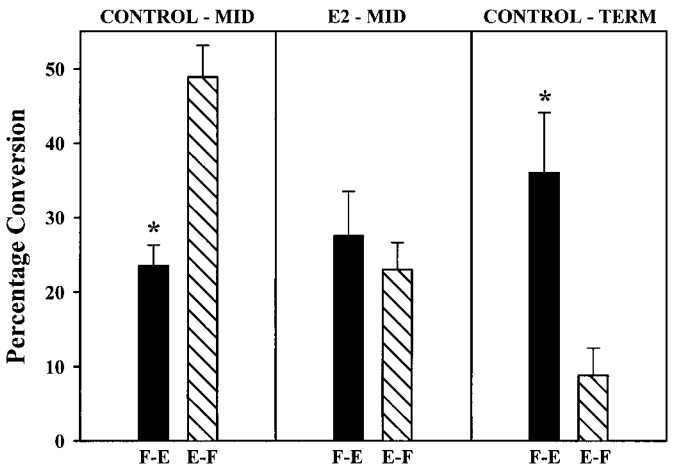

FIG. 1. Transuteroplacental interconversion (%) of cortisol (F) and cortisone (E) in untreated baboons at midgestation (CONTROL-MID) and term (CONTROL-TERM), and in baboons treated with androstenedione for 30 days to elevate placental estrogen production at midgestation (E2–MID). Values are the mean ± SEM (n = 4–5 per group). Asterisk indicates that the percentage conversion of F to E differs ($p < 0.05$) from that of E to F. Redrawn from Pepe et al. [69].

dehydrogenase minus 11-oxoreductase) in the labyrinth zone (the major site of maternal-fetal exchange) fell between Days 16 and 22 of pregnancy (term = Day 23), over the same period the net activity increased in the basal zone (the major site of placental steroid and peptide hormone synthesis) [60]. Consistent with these changes in bioactivity, 11β-HSD-1 mRNA expression increased dramatically in the labyrinth zone, while that for 11β-HSD-2 increased in basal zone but almost completely disappeared from the labyrinth zone [13, 60] (see Fig. 2). Further studies are required to establish whether similar regional differences exist in the patterns of placental 11β-HSD-1 and -2 expression in other species. Interestingly, Pepe et al. [55] have proposed that regional distribution of the two enzymes occurs within baboon placenta, since immunoreactive 11β-HSD-2, but not 11β-HSD-1, was lost following collagenase dispersion. Moreover, an apparent shift in 11β-HSD-2 immunolocalization away from the apical region of syncytiotrophoblast was evident with advancing gestation [55].

Regulation of Placental 11β-HSD

The changing expression patterns of 11β-HSD-1 and -2 in the adjacent zones of the rat placenta [13, 60], and the gestational increases in placental 11β-HSD bioactivity in other species [7, 55, 61, 68], suggest that the 11β-HSD proteins are highly regulated in a tissue-specific manner. In the baboon, experimental elevation of placental estrogen synthesis at midgestation was shown to alter cortisol/cortisone metabolism in vivo [69] (see Fig. 1) and placental 11β-HSD activity in vitro [53] to more closely approximate that observed at term pregnancy. Moreover, treatment of cultured baboon syncytiotrophoblast with estrogen in vitro increased 11β-dehydrogenase bioactivity [52]. Collectively, these studies suggest that estrogen may be the primary regulator of placental 11β-HSD in the baboon, consistent with recent observations that estrogen potently up-regulates both 11β-HSD-1 and -2 expression in the nonpregnant rat uterus [28]. Whether estrogen has a similar regulatory role in the rat placenta is uncertain, but estrogen levels do rise progressively toward term in this species [70], coincident with marked changes in placental 11β-HSD expression. Other

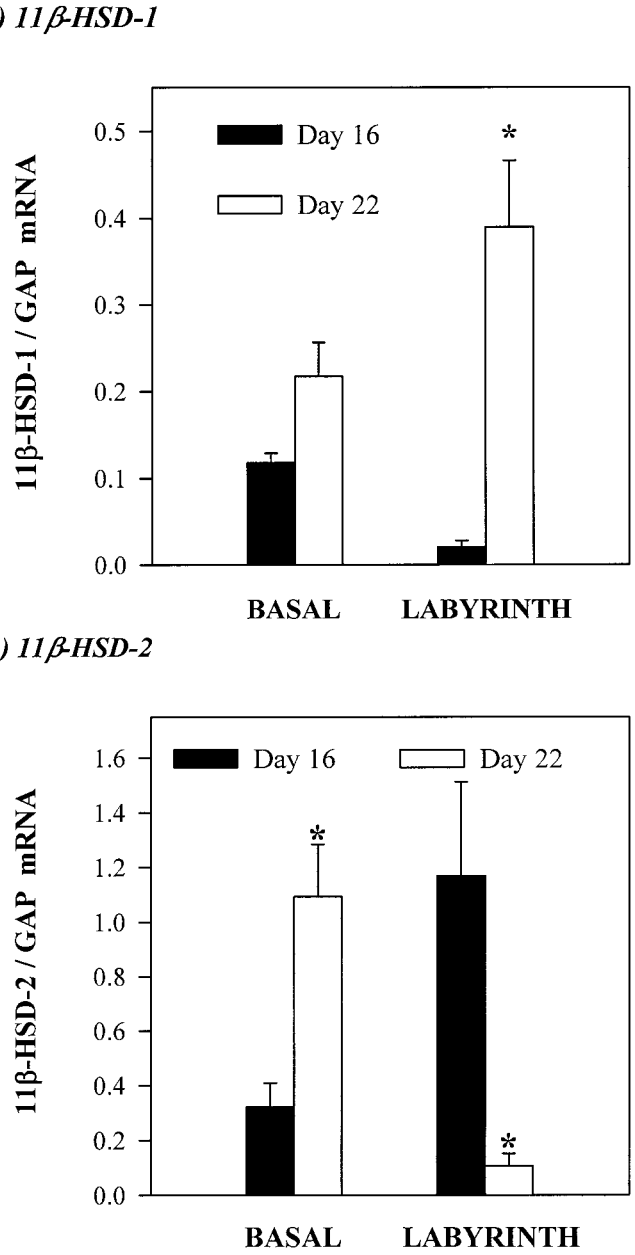

FIG. 2. Changes in placental basal and labyrinth zone expression of **a**) 11β-HSD-1 and **b**) 11β-HSD-2 mRNA transcripts between Days 16 and 22 of rat pregnancy (term = Day 23). The 11β-HSD-1 and 11β-HSD-2 mRNAs were measured by S1 nuclease protection assay and normalized to the corresponding glyceraldehyde-3-phosphate dehydrogenase (GAP) signal. Values are the mean ± SEM (n = 3 per group). * $p < 0.05$ compared with corresponding Day 16 value (unpaired *t*-test). Although 11β-HSD-1 mRNA expression in the basal zone appeared to increase between Days 16 and 22, the increase just failed to reach statistical significance ($p = 0.071$). Redrawn from Burton et al. [60].

possible regulatory factors include steroids (e.g., progestins and androgens) or peptide hormones (e.g., rat placental lactogens) produced locally in the placenta operating in a paracrine manner. Since hormone production occurs primarily in the basal zone of the rat placenta [71], such paracrine regulation could also account for the differences in 11β-HSD-2 expression between the two zones. Sun et al. [65] have recently shown that progesterone inhibits 11β-HSD-2 mRNA expression in human syncytiotrophoblasts in vitro, and kinetic inhibition of placental 11β-HSD activity by progesterone has long been recognized [47, 72].

Functional Significance of Placental 11β-HSD

a) The placental glucocorticoid barrier. The function of placental 11β-HSD is obviously dependent on the dominant direction of the catalyzed reaction (11-oxoreductase vs. 11β-dehydrogenase activity) in vivo, but as discussed above, enzyme lability in vitro has led to uncertainties in this regard. For this reason, some of the most instructive experiments relating to the function of placental 11β-HSD are the series of studies by Pepe and coworkers [68, 69, 73, 74] in which the fate of maternally or fetally infused radiolabeled cortisol and cortisone was followed. This approach provides an indirect measure of 11β-HSD bioactivity in vivo, thus retaining the normal range of substrate concentrations while avoiding problems associated with cell dispersion or disruption. These studies demonstrated that the placenta can serve as a barrier to the transfer of maternal glucocorticoids to the fetus, as originally proposed by Osinski [43]. Importantly, however, they also revealed the dynamic nature of this placental glucocorticoid barrier, which although possibly species-specific has provided an important conceptual framework in which to consider its physiological implications. Moreover, the incompleteness of this barrier, first highlighted by these in vivo studies, is now a crucial part of our understanding of the fetal glucocorticoid environment and its implications for fetal growth and subsequent development of disease in adult life [75] (see below).

The main thrust of the baboon studies alluded to above is that transfer of active glucocorticoid from mother to fetus is relatively high at midgestation compared with late pregnancy. Indeed, comparison of the relative specific activities of radiolabeled cortisol in maternal and fetal compartments shows that at midgestation, effectively all of the cortisol present in the fetal circulation is maternal in origin, consistent with the absence of 3β-HSD expression in the fetal adrenal at this time [68]. Pepe and colleagues [68, 69, 74, 76] have hypothesized that as pregnancy progresses, this transfer of maternal cortisol to the fetus is restrained by estrogen-induced up-regulation of placental 11β-HSD, thereby increasing the placental glucocorticoid barrier. This in turn initiates development of the fetal HPA axis and thus promotes fetal autonomy. Interestingly, the rat placenta appears to exhibit the reverse pattern with respect to the placental glucocorticoid barrier, since 11β-HSD-2-specific bioactivity [13] and mRNA expression [13, 60] almost completely disappear in the labyrinth zone (the exchange area of the placenta) near term. This might appear counterintuitive given the potentially harmful effects of excess glucocorticoid exposure on fetal growth and subsequent development of adult disease; by this late stage of pregnancy, however, the rodent fetus has developed an effective HPA axis and considerable 11β-HSD-2 is expressed in various fetal organs [77], presumably allowing the fetus to cope with increased exposure to maternal glucocorticoids. Indeed, the latter could be advantageous to the fetus, since glucocorticoids promote the maturation of organ systems crucial for the successful transition to extrauterine life [3].

The question remains, however, as to why the opposite pattern of change occurs in the placental glucocorticoid barrier with advancing pregnancy in the rodent versus the primate. We have proposed [13] that it may relate to the evolution of a fetoplacental unit for estrogen synthesis in the higher primates (suborder Anthropoidea). The basis of the fetoplacental unit is the placental utilization of fetal adrenal androgens for estrogen synthesis [78]; the rise in this synthesis with advancing gestation reflects, in part, increased fetal androgen supply (for reviews see [68, 79]). Given that the trophic drive for this increase in fetal adrenal androgen secretion is at least in part fetal pituitary adrenocorticotropic hormone, the loss of a placental glucocorticoid barrier and the associated passage of maternal glucocorticoids to the fetus would inhibit the fetal HPA axis and thus the supply of androgens to the placenta. This in turn would compromise the normal increase in placental estrogen synthesis that occurs late in primate pregnancy and is crucial for parturition [80]. In contrast, the rise in maternal estrogen observed near term in the rat is ovarian in origin [70] and thus not dependent on fetal adrenal status.

In addition to its proposed role in development of the fetal HPA axis, variations in placental 11β-HSD activity in the rat have been related to fetal growth and subsequent development of disease in adult life [8, 59, 81–83]. A large epidemiological study showed that adult humans with low birth weight in combination with large placental weight were at risk of developing hypertension [84]. It was proposed that this relationship may reflect increased exposure of the fetus to maternal glucocorticoids [8], since Benediktsson et al. [59] had found that rat placental 11β-dehydrogenase activity was positively correlated with term fetal weight and negatively correlated with placental weight. A positive association between birth weight and placental 11β-HSD activity has also been observed in the human [51]. Moreover, offspring of rats treated with the synthetic glucocorticoid dexamethasone during pregnancy had lower birth weights and higher adult blood pressure than offspring of control rats [59]. In contrast, inhibition of endogenous maternal and fetal glucocorticoid synthesis with maternal metyrapone treatment over the last week of pregnancy enhanced fetal growth by around 10% [9].

Collectively, the effects of these experimental manipulations of fetal glucocorticoid exposure suggest a critical role for placental 11β-HSD in the control of normal fetal growth and the subsequent development of adult disease. Accordingly, when 11β-HSD activity was inhibited by administration of carbenoxolone to rats throughout pregnancy, fetal growth was impaired and offspring became hypertensive [82] and exhibited hyperglycemia [83] as adults. Because these effects were dependent on the presence of the maternal adrenals, they presumably resulted from increased exposure of the fetus to maternal glucocorticoids associated with inhibition of placental 11β-HSD. Indeed, the ratio of radiolabeled corticosterone to 11-dehydrocorticosterone in fetuses of carbenoxolone-treated mothers infused with radiolabeled corticosterone was higher than in sham-treated controls [83], indicative of a reduction in the placental glucocorticoid barrier.

b) Placental 11β-HSD as modulator of glucocorticoid and progesterone actions. Placental 11β-HSD may also locally regulate access of glucocorticoids to their receptors within the placenta. Binding studies have demonstrated the presence of placental GR in several species including rodents [11, 12], rabbits [85], and humans [86–88]; and in the rat, comparable amounts of the GR are present in extracts of basal and labyrinth zones [12], consistent with recent observations of GR mRNA expression in these two regions [13].

Glucocorticoids could potentially affect a wide range of cellular functions within the placenta, from trophoblast differentiation soon after implantation to hormone synthesis in the fully formed placenta. In the rat, the basal zone of the placenta is the major site of peptide and steroid hor-

mone synthesis, and changes in 11β-HSD-1 and -2 expression in this zone are likely to reduce the concentration of active glucocorticoid near term [13, 60]. This reduction may contribute to the fall in basal zone 17α-hydroxylase expression that occurs near term [89], since glucocorticoids are known to stimulate 17α-hydroxylase in sheep placenta [90]. In contrast, glucocorticoids are potent inhibitors of prostaglandin synthesis and metabolism (for review see [91]), and inhibition of prostaglandin dehydrogenase (PGDH) activity by glucocorticoids was recently demonstrated in human placenta [92]. Thus, reduced basal zone glucocorticoid levels associated with 11β-HSD-1 and -2 changes may facilitate the dramatic increase in PGDH activity that occurs in this zone over the last 4 days of rat pregnancy [93]. Indeed, an opposite shift in the activity of PGDH occurs over the same period in the labyrinth zone, where active glucocorticoid levels are likely to increase due to reduced 11β-HSD-2 expression near term. Opposite changes in the two placental zones also occur in the synthesis of placental lactogen-II late in rat pregnancy, with an increase observed in the labyrinth zone and a decrease in the basal zone [94], raising the possibility that placental lactogen-II synthesis in the rat placenta is modulated by glucocorticoids and thus by 11β-HSD-1 and -2 expression.

There may also be a number of interactions between glucocorticoids and progesterone within the placenta, such as that recently demonstrated by Karalis et al. [10] in which the inhibition of corticotropin-releasing hormone synthesis by progesterone in cultured human trophoblasts was blocked by cortisol. This effect of progesterone may be mediated via the GR rather than the progesterone receptor (PR) [10], since there remains controversy as to whether PR is expressed by human trophoblast (e.g., see [10, 95]). Although the rat placenta does not produce corticotropin-releasing hormone, progesterone does have other important effects on placental function in this species, most notably with respect to growth [96]. Moreover, while mRNA for the GR has been localized to both placental zones [13], PR appear to be expressed only in the basal zone [97]. This raises the possibility that progesterone effects in the labyrinth zone may be mediated via the GR and as such could be susceptible to inhibition by glucocorticoids as occurs in human placental trophoblasts [10]. Progesterone action via the GR was recently shown to be critically important in relation to regression of the rat corpus luteum near the end of pregnancy [98], and the dramatic induction of luteal 11β-HSD-2 at this time [40] is likely to regulate physiological competition between progesterone and corticosterone for access to the GR. Thus, 11β-HSD-2 may play a role in mediating interactive effects of progesterone and glucocorticoids within the placenta similar to that demonstrated for the corpus luteum.

DISCUSSION

In conclusion, 11β-HSD appears to play two distinct roles in the placenta—one in maintaining the placental glucocorticoid barrier between mother and fetus, and the other in modulating local actions of glucocorticoids and possibly progesterone within the placenta. Developmental changes in the completeness of the glucocorticoid barrier are important for fetal growth, development of the fetal HPA axis, and the final maturation of fetal organ systems. Moreover, given the pleiotypic effects of glucocorticoids on development, aberrations in the placental glucocorticoid barrier can profoundly influence the subsequent onset of disease in adult life. Since placental glucocorticoid metabolism also determines local concentrations of active glucocorticoid, we suggest that placental expression of the 11β-HSD enzymes provides an important mechanism to regulate activation of the placental GR. Furthermore, recent reports showing that some progesterone effects are exerted via the GR suggest an additional role for placental 11β-HSD in regulating progesterone-glucocorticoid competition for access to GR, which in turn could impact on a wide range of placental functions.

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