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31. Pregnancy and Lactation

MINERALOCORTICOSTEROIDS AND PREGNANCY: REGULATION OF EXTRA-ADRENAL DEOXYCORTICOSTERONE PRODUCTION BY ESTROGEN

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Summary—During pregnancy, deoxycorticosterone (DOC) in maternal plasma is produced principally by 21-hydroxylation of circulating progesterone in a number of extra-adrenal tissues. Estrogen acts, directly or indirectly, to increase the transfer constant of conversion of progesterone to DOC. In this study, we evaluated the regulation of DOC production during pregnancy by considering the plasma levels of progesterone, the kinetics of extra-adrenal steroid 21-hydroxylase, and the stimulation of the conversion of progesterone to DOC by estrogen.

INTRODUCTION

During pregnancy in women, the concentrations of deoxycorticosterone (DOC), a potent mineralocorticosteroid, increase strikingly. Indeed, in near-term pregnant women, the levels of DOC in plasma are as much as 50 times those in plasma of men and non-pregnant women [1–8]. The origin of such massive amounts of DOC during pregnancy is believed to be principally by way of the extra-adrenal 21-hydroxylation of progesterone since it is known that plasma progesterone is converted to DOC in men, nonpregnant and pregnant women, and adrenalectomized people [9]. But more than that, steroid 21-hydroxylase activity is demonstrable in a number of tissues [10–13], many of which are known to be mineralocorticosteroid-responsive tissues, e.g. kidney, aorta, spleen, and thymus. Also, it is known that the transfer constant of conversion of progesterone to DOC is increased in response to the action of estrogen [14] by a mechanism that, as yet, is undefined. In this study, we considered in detail the biochemical mechanisms that are involved in the regulation of extra-adrenal 21-hydroxylation of progesterone, and thence the fractional conversion of progesterone to DOC, during pregnancy.

EXPERIMENTAL

The methods of procedure for the conduct of the studies reviewed in this investigation are described in detail elsewhere. Specifically, the transfer constant of conversion of progesterone to DOC was determined by use of the *in vivo* internal standard technique as described [9]. The specific activity of steroid 21-hydroxylase was determined in microsome-enriched fractions of human tissues as described [10–13]. The concentrations of progesterone and DOC in plasma were determined by use of specific radioimmunoassays as described [7].

RESULTS

During pregnancy, the production rate of DOC is dependent on (1) the transfer constant of conversion of progesterone to DOC, which is known to vary widely among individual people and (2) the plasma levels of progesterone. In turn, the transfer constant of progesterone to DOC is modulated by estrogen. The findings of a number of investigations are indicative that the extreme hyperestrogenism that is associated with human pregnancy gives rise to increased formation of DOC in extra-adrenal tissues by way of the 21-hydroxylation of plasma progesterone. The evidence in support of this is as follows:

(1) The administration of diethylstilbestrol to women pregnant with a dead fetus is associated with an increase in the transfer constant of conversion of progesterone to DOC in extra-adrenal tissue(s) [14].

(2) The levels of DOC in the plasma of women with pregnancies that are characterized by hypoestrogenism, viz. those in which there is an anencephalic fetus, are decreased compared with those in women with normal pregnancies of comparable gestational age [15].

(3) The concentrations of DOC in umbilical cord plasma of anencephalic fetuses is decreased compared with that in umbilical cord plasma of normal fetuses, whereas plasma levels of progesterone are similar [15].

(4) The administration of diethylstilbestrol to a woman pregnant with an anencephalic fetus leads to an increase in the plasma levels of DOC [15].

(5) The specific activity of steroid 21-hydroxylase in microsome-enriched fractions of fetal kidney tissues obtained from anencephalic fetuses is decreased compared with that in similar preparations of kidney tissues obtained at midtrimester from normal fetuses [16].

(6) In two women with pregnancies characterized

by hypoestrogenism, i.e. fetal demise, the transfer constant of conversion of progesterone to DOC was similar to or decreased (by 25–30%) compared with that which was determined in the same woman several months postpartum [9].

DISCUSSION

As stated, the production rate of DOC in pregnant women is believed to be dependent principally on two factors. First, the findings of a number of studies are supportive of the view that estrogen acts, either directly or indirectly to stimulate the activity of the enzyme(s) that catalyzes the conversion of progesterone to DOC. The evidence in favor of this proposition is based on diverse studies conducted both *in vivo* and *in vitro*. Second, there is evidence that the fractional conversion of progesterone to DOC is constant until plasma levels of progesterone reach an amount that is saturating for the enzyme(s); based on analysis of enzyme kinetics *in vitro*, this value is estimated to be >75 ng/ml [14]. Thus, during the latter part of pregnancy, the hormonal milieu of women may affect profoundly the biochemical mechanisms that lead to the formation of DOC. Yet, at the same time, the end result of these various effectors may be such that the transfer constant of the conversion of progesterone to DOC is, coincidentally, unchanged. On the one hand, the rate of production of progesterone by the placenta increases such that the enzyme(s) that catalyzes 21-hydroxylation of progesterone becomes saturated with substrate. On the other hand, the formation of estrogen, produced in the placenta principally from dehydroisoandrosterone sulfate (which arises in the fetal adrenal gland and is produced in increasing concentrations with gestational age) also is increasing [17, 18]. Thus, taken together, it seems reasonable to predict that the transfer constant of conversion of progesterone to DOC would be altered by these several factors. Namely, the high levels of progesterone would serve to lower this value, whereas the action of estrogen serves to increase the value in a given woman. We suggest that, in fact, this is the case but that there may be additional factors that come to bear on the fractional conversion of progesterone to DOC in women. In this context, it is important to recall that the activity of steroid 21-hydroxylase is demonstrable in a number of tissues *in vitro* [10–13]. It can be envisioned that the expression, and thence the activity, of the cytochrome P-450 that catalyzes steroid 21-hydroxylation in one tissue could be increased in response to the action of estrogen, whereas that in another tissue may not be responsive to estrogen. But more than that, it also can be envisioned that the contribution of various tissues to the total extra-adrenal production of DOC is altered during pregnancy compared with that in a given woman at a time when she is not pregnant. For example, during pregnancy and associated with the characteristic increase in plasma volume, there is a massive increase in the amount of vascular tissue. Since the specific activity of steroid 21-hydroxylase is known to be high in this tissue [12], it is likely that the contribution of this tissue to the total production of DOC is increased. Conversely, it may be that the contribution of other tissues is decreased during pregnancy.

Based on all of these considerations, we suggest that during pregnancy, the transfer constant of conversion of progesterone to DOC is affected by a number of factors that include hormonal, anatomic, and physiological changes. As a result of these various factors, it can be envisioned that the transfer constant of conversion of plasma progesterone to DOC in a pregnant woman may be similar to that in the same woman at a time when she is not pregnant, but that the similarity is coincidental.

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