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AFFINITY OF RU 486 AND ITS METABOLITES FOR HUMAN PROGESTERONE AND GLUCOCORTICOID RECEPTORS

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Introduction: RU 486 is a promising new antiprogesterone and antiglucocorticoid.We have compared the affinities of the monodemethylated, didemethylated and alcoholic non-demethylated metabolites of RU 486 with the parent steroid, progesterone, ORG-2058 and dexamethasone for progesterone and glucocorticoid binding proteins.
Materials and methods: The progesterone receptor studies were performed with human myometrium and endometrium using 3H-ORG-2058 as tracer in the presence of a 100-fold excess of cortisol. Placenta was used for the glucocorticoid receptor studies. The tracer was 3H-dexamethasone and a 100-fold excess of progesterone was used.
Results: The affinities for the progesterone bindning protein were: ORG-2058 > RU 486 > progesterone > monodemethylated metabolite > alcoholic metabolite > didemethylated metabolite. The affinities for the glucocorticoid bindning protein were: dexamethasone > didemethylated metabolite > alcoholic metabolite > RU 486 > monodemethylated metabolite .
Discussion: Our results indicate that some metabolites of RU 486 in human have higer affinity for glucocorticoid bindning protein than the parent compound. Since the plasma levels of the metabolites after oral ingestion of 50 - 200 mg are in the micromolar range, and close to those of the parent compound, their biological significance is evident.

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INTERACTION OF ANTIPROGESTINS WITH UTERINE NUCLEAR AND CYTOSOL PROGESTERONE RECEPTORS.

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The effect of antiprogestins STS 557,5α-dihydronorethindrone (5α-DNE) and 5α-dihydronorgestrel (5α-DNG) on uterine progesterone receptors was studied in ovariectomized hormone primed rats and compared with progesterone treatment effect. The level of cytosolic progesterone receptors (PRC) in 0.5 mg progesterone (P) treated group was 101 fm/mg DNA and nuclear receptors (PRn) was 4770 fm/mg DNA with a nuclear:cytosol receptor ratio of 47.2. The nuclear:cytosol ratio increased with increasing doses of P (0.5 mg,1mg and 2 mg) to 238.2. Under the influence of antiprogestin STS 557, 5α-DNE and 5α-DNG PRC was 252, 377 and 127 fm/mg DNA respectively. The level of PRn was 7411, 17925 and 3030 in STS 557, 5α-DNE and 5α-DNG treatment groups.A similar pattern of highest receptor concentration due to 5α-DNE and lowest due to 5α-DNG was obtained from total receptor level. The nuclear:cytosol receptor ratio of 5α-DNE group (47.5) was comparable with 0.5 mg P group (47.2) while the ratio decreased to 29.4 in STS 557 group and to 23.8 in 5α-DNG group. Based on this,5α-DNG and STS 557 appeared to be better antiprogestins than 5α-DNE. The concentration of PRn in decidual tissue decreased maximally due to the effect of 5α-DNG as compared to non-decidual control,being 617 fmoles/mg DNA followed by STS 557 (3180) and 5α-DNE (3740). A maximal decrease in PR level(4.6 fm/mg DNA) was observed in the cytosol of decidual tissue due to 5α-DNG effect. The results suggest that antiprogestins may be effective in terminating early pregnancy by bringing about a decrease in the nuclear and cytosol progesterone receptor levels.