Antiprogestagen Activity of 5H-Progesterone Metabolites and Their Analogues, 16α,17α-Cyclohexane-5H-Pregnan-3,20-Diones

E. N. Kareva, A. V. Kamernitskii*, I. S. Levina*, N. V. Kirpichnikova, L. E. Kulikova*, and V. V. Podval'nyuk

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Antiprogestin activity of 5H-progesterone metabolites and their analogues 16α,17α-cyclohexan-5H-pregnan-3,20-diones was tested on rats. Modified pregnancy interruption test showed that 5α(H)-isomers of natural and synthetic hormones exhibit maximum activity.

Key words: *antiprogestin activity; pregna-D'-pentaranes*

The search for new selective antihormonal drugs is very important for medicine. In particular, antagonists of steroid hormones regulating pregnancy (progestins) are widely used in oncogynecology and obstetrics. However, 19-norantiprogestins including their main representative, mifepristone (RU-486), possess pronounced antiandrogen and antiglucocorticoid activity, which limits their clinical application. Therefore, the search for specific and selective progestagens is of special importance. New progesterone derivatives, pregna-D'-pentaranes bearing additional D' carbocycle were synthesized at the N. D. Zelinskii Institute of Organic Chemistry. These compounds, especially 16α, 17α-cyclohexanprogesterone are highly selective ligands of progesterone receptors [1,3,5]. Moreover, further experiments demonstrated that reduction of double bond in the A ring typical for progesterone and its analogues exhibiting progestin activity converts 16α, 17α-cyclohexanprogesterone into 16α,17α-cyclohexan-5H-pregnandiones possessing no progestin activity, but completely inhibiting the effect of progesterone in experimental animals [4]. Since these 5H-compounds are analogues of natural progesterone metabolites (dihydroprogesterones), it was interesting to compare their antiprogestin in the pregnancy interruption test in rats. We also examined two pregna-D'-pentaranes: 16α,17α-cyclopropanoprogesterone showing high activity in the endometrium proliferation test (Clauberg—McFale test) and low activity in pregnancy maintenance, and 16α,17α-cyclohexo-2'-enoprogesterone with low proliferative effect, but highly active in pregnancy maintenance test [1].

MATERIALS AND METHODS

The following compounds were tested: 16α,17α-cyclohexan-5α-pregnan-3,20-dione, 16α,17α-cyclohexan-5β-pregnan-3,20-dione, 16α,17α-cyclopropanoprogesterone, 16α,17α-cyclohex-2'-enoprogesterone synthesized at the Institute of Organic Chemistry [3], and their structural analogues, natural progesterone metabolites: 5α-dihydroprogesterone (5α-(H)-pregnan-3, 20-dione) and 5β-dihydroprogesterone (5β-(H)-pregnan-3,20-dione) (Sigma). Structures of these compounds are presented on Fig. 1. Antiprogestin activity of test substances was compared with that of mifepristone (RU-486) (Exelgyn).

Antiprogestin activity was evaluated on albino female rats weighing 160-190 g with 4-5-day estrous cycle. Each experimental and control group consisted of 15 animals. Test drugs (10 mg/kg, oil solution)

Department of Molecular Pharmacology and Radiobiology, Medical Biological Faculty of the Russian State Medical University; *Group of Steroid and Oxylipin Chemistry, N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Science, Moscow

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were injected intraperitoneally starting from day 7 of pregnancy for 3 days. On day 10 the animals were euthanized with ether and the uterine horns were dissected. The number of implantation sites seen as bearded enlargements of the uterus was counted. The animals receiving only solvent were used as control. Antiprogestagen activity was estimated by the number of lyzed fetuses in experimental groups, the results are presented as $M \pm m$. Statistical processing of the results was performed using Student t test.

RESULTS

The percentage of lyzed fetuses in rats treated with mifepristone was 100.0±4.9, while for 16α,17α-cyclohexan-5α-pregnan-3,20-dione, 16α,17α-cyclohexan-5β-pregnan-3,20-dione, 5α-dihydroprogesterone, 5β-dihydroprogesterone, 16α,17α-cyclopropanopregn-4-en-3,20-dione, and 16α,17α-cyclohex-2'-enopregn-4-en-3,20-dione the corresponding values were 66.0±3.3, 33.0±1.9, 60.0±3.6, 45.0±2.3, 23.0±1.2, and 17.0±0.9% fetuses, respectively, compared to 0.0±0.6% in the control.

Thus, mifepristone showed maximum antiprogestin activity, which agrees with previous data [7]; 16α,17α-cyclohexano-5α-pregnan-3,20-dione and 5α(H)-dihydroprogesterone possessing similar antiprogestin effect were superior to 5β(H)-isomeres, which confirms our previous data [2]. Antiprogestin activity of 5β(H)-isomeres with cis-bond between A and B rings was only 50% of activity of 5β-dihydroprogestrone (native progesterone metabolite) and one-third of its α-analogue. Pentaranes showed similar minor antiprogestin effects, but differed by their action on endometrium proliferation and pregnancy maintenance in ovariectomized animals [1].

Since the interaction of 5α(H)-compounds with progesterone receptors is much weaker than that of mifepristone, high antiprogestin activity of these compounds is of special interest [6]. Thus, 16α,17α-cyclohexan-5α(H)-pregnan-3,20-dione can present practical interest because of its significantly lower affinity to androgen and corticoid receptors compared to mifepristone.

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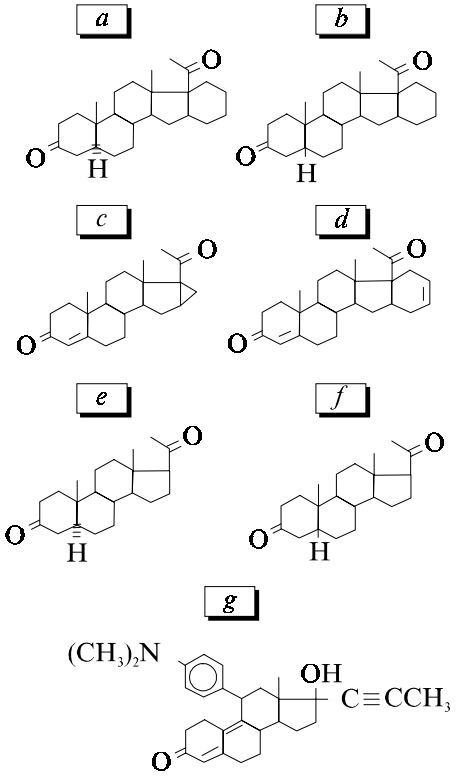

Fig. 1. Structure of 16α,17α-cyclohexan-5α-pregnan-3,20-dione (*a*), 16α,17α-cyclohexan-5β-pregnan-3,20-dione (*b*), 16α,17α-cyclopropanoprogesterone (*c*), 16α,17α-cyclohex-2-enoprogesterone (*d*), 5α-dihydroprogesterone (*e*), 5β-dihydroprogesterone (*f*), and reference drug mifepristone (*g*).

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