CONTRACEPTIVE ACTIVITY OF COMBINATIONS OF STEROID AND ANTIADRENERGIC PREPARATIONS

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Experiments on sexually mature female rats showed that daily simultaneous administration of mestranol (0.04 mg/kg) and megestrol acetate (0.8 mg/kg) by gastric tube for 14 days had no appreciable contraceptive effect, whereas administration of the steroids in the same doses combined with antiadrenergic drugs α-methyldopa (100 mg/kg) or pyrroxan (10 mg/kg) effectively prevented pregnancy.

KEY WORDS: contraceptive activity; steroid preparations; antiadrenergic drugs.

Considerable attention has recently been paid in other countries to the question of central adrenergic control over reproductive function and, in particular, to the study of possible pharmacological interference with the adrenergic mechanisms controlling ovulation [6, 8, 9]. Data in the literature indicate that some adrenoblockers or inhibitors of catecholamine biosynthesis inhibit ovulation appreciably [3, 12, 13]. On the other hand, in order to minimize side effects of steroid contraceptives, ways of reducing the doses of their estrogenic and progestagenic components must be sought. In this connection it is interesting to study the possibility of potentiating the contraceptive effect of steroids used in small doses by administering them in conjunction with antiadrenergic agents.

This paper describes the results of experiments to study the contraceptive activity of the estrogen–progestagenic components of the combined preparation megestranol, used in a new ratio (1:20) and in minimally effective doses, in conjunction with α-methyldopa, an inhibitor of dopamine and noradrenalin biosynthesis, or with the Soviet adrenoblocker pyrroxan.

EXPERIMENTAL METHOD

Experiments were carried out on 83 sexually mature female rats weighing 180-200 g with a normal 4-5-day estrous cycle. All drugs were given by gastric tube once a day for 14 days. There were eight series of experiments. In series I (control) the animals were given distilled water, in series II mestranol (0.04 mg/kg) and megestrol acetate (0.8 mg/kg), in III α-methyldopa (100 mg/kg), and in IV α-methyldopa (100 mg/kg) combined with mestranol and megestrol acetate in the same doses. In the next four series the contraceptive activity of pyrroxan (10 mg/kg) and also of a combination of it with mestranol (0.04 mg/kg) and megestrol acetate (0.8 mg/kg) was studied. The corresponding control series also was set up. On the third day of administration of the drugs copulation was allowed. The day on which spermatozoa were found in the vagina was taken to be the first day of pregnancy. The presence or absence of pregnancy (contraceptive effect) was determined by diagnostic laparotomy performed on the 9th day after copulation. A second laparotomy was performed 2 days before parturition and the contraceptive effect of the preparations was judged from maintenance of the number of fetuses and the corpora lutea. The effect of the antiadrenergic drugs α-methyldopa and pyrroxan on the noradrenalin level in the hypothalamus of the rats also was determined. The drugs were given to the animals daily for 14 days by gastric tube. The noradrenalin content was determined fluorometrically by the method of Euler and Floding [7] in Govyrin's modification [1]. The results were subjected to statistical analysis.

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TABLE 1. Effect of Antiadrenergic Agents on Noradrenalin Level in Rat Hypothalamus

Substance	Dose (mg/kg)	No. of expts.	Noradrenalin (μg/g)	P relative to control
α-Methyl dopa	100	5	0,33±0,08	<0,001
Pyrroxan	10	7	0,93±0,3	>0,5
Control		6	1,10±0,08	

EXPERIMENTAL RESULTS

Administration of mestranol and megestrol acetate in small doses for 14 days to the rats caused no appreciable change in the character or duration of the estrous cycle. The cycle also was unchanged when a combination of steroid preparations in the same doses and α-methyldopa was used, and also when α-methyldopa and pyrroxan were given separately. Only when a combination of pyrroxan and steroid hormones was given was the estrous cycle significantly lengthened compared with the control, a result mainly due to lengthening of the resting state (diestrus–metestrus). Whereas in the intact rats the duration of the cycle was 4.0 ± 0.11 days, in animals receiving a combination of these substances it was 6.0 ± 0.5 days ($P < 0.05$).

Administration of steroid preparations in small doses to the rats had no significant contraceptive effect. Some contraceptive action (28.5%) was found with α-methyldopa but statistical analysis showed a low level of significance ($P = 0.1$).

Completely different results were obtained by combined administration of mestranol, megestrol acetate, and α-methyldopa in the same doses: by the time of the first laparotomy 75% of the rats were still not pregnant ($P = 0.01$). Administration of small doses of steroids simultaneously with the adrenoblocker pyrroxan also was effective. In this series of experiments pregnancy was absent in 50% of the inseminated animals ($P = 0.05$). Meanwhile administration of pyrroxan alone did not prevent the onset of pregnancy (all the animals were pregnant). Determination of the noradrenalin content in the hypothalamus of rats receiving pyrroxan for 14 days showed no significant change in the level of the mediator (Table 1). Administration of α-methyldopa, inhibiting catecholamine biosynthesis, to the animals for the same period, however, led to a marked decrease (by 70%) in the noradrenalin content in the hypothalamus ($P < 0.001$).

The contraceptive action of megestranol, a combination of mestranol and megestrol acetate in the ratio of 1:50, is based primarily on the inhibition of ovulation resulting from the inhibitory effect of the preparation on secretion of the pituitary luteinizing hormone [2, 4, 5, 10]. The absence of any appreciable contraceptive effect when the components of megestranol were given in a different ratio and in small doses in the present experiments can be explained on the grounds that these doses were too small to inhibit ovulation. Administration of mestranol and megestrol acetate in the same doses, together with antiadrenergic substances (α-methyldopa or pyrroxan), however, led to a marked increase in the contraceptive effect, evidently linked with the antiovulatory effect both of the steroids and of the antiadrenergic preparations. By actively modifying catecholamine metabolism in the hypothalamus (reducing the noradrenalin level, as the present experiments confirmed), α-methyldopa simultaneously blocks ovulation [12]. Pyrroxan, an α-adrenergic blocking agent, inhibits the adrenergic systems of the hypothalamus and by that means it may possibly have a definite effect on the central mechanisms regulating ovulation. According to Shally et al. [14], α-adrenoblockers (phenoxybenzamine, etc.), which block central adrenergic systems, stimulate dopamine metabolism in the median eminence of the hypothalamus; in their opinion this results in inhibition of secretion of the luteinizing hormone releasing factor. An interesting suggestion has recently been made that the inhibitory action of steroids (mestranol, ethinylestradiol, derivatives of 19-nortestosterone) themselves on ovulation is partly due to their effect on dopamine metabolism in the dopaminergic neurons of the hypothalamus [11]. The marked contraceptive effect of a combination of these preparations revealed by the present experiments must evidently be interpreted in the light of these data. Another point to note is that the combined use of antiadrenergic drugs (α-methyldopa, pyrroxan), with their known hypotensive action, and of steroid preparations for contraceptive purposes may at the same time prevent the elevation of the blood pressure produced by some hormonal contraceptives. Further experimental research into the efficacy of such combinations could therefore prove useful.

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