EFFECT OF ADIPHENINE ON PITUITARY GONADOTROPIC FUNCTION

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In experiments on rats the nicotine-like cholinolytic preparation adiphenine in doses of 10-16 mg/kg increased the output of pituitary follicle-stimulating hormone, at the same time depressing the lactogenic and luteinizing activity of the pituitary. With an increase in the dose to 80 mg/kg, adiphenine had an action similar to that of the muscarine-like cholinolytic methyldiazine, probably because adiphenine also possesses muscarine-like cholinolytic properties.

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Previous experiments on rats showed that the central muscarine-like (m-) cholinolytic methyldiazine causes delay in sexual maturation of immature animals, inhibition of estrus, and a decrease in the content of gonadotropins in the pituitary [2-4], and also the phenomenon of stimulation of mammary gland growth and lactation.

In the present investigation the effect of the nicotine-like (n-) cholinolytic adiphenine was studied on the follicle-stimulating, luteinizing, and luteotropic functions of the pituitary.

Adiphenine (trasentin) belongs to the class of central cholinolytics with the property of selectively blocking n- cholinergic systems of the brain [1].

EXPERIMENTAL METHOD

A series of chronic experiments was carried out on 118 sexually immature rats of both sexes (weight 40-80 g) and 142 adult females rats (150-200 g). The effect of adiphenine on gonadotropic function was assessed from the following criteria: 1) action on maturation of the sexual apparatus of immature rats of both sexes (weight 60-80 g); 2) effect on estrous function of adult female rats (weight 150 g); 3) effect on content of gonadotropins in the pituitary; and 4) effect on lactogenic function of the pituitary.

EXPERIMENTAL RESULTS

The results of experiments to study the action of adiphenine on maturation of the sexual apparatus of immature rats showed that in a dose of 10-40 mg/kg the drug had no significant effect in females but slightly stimulated growth of the sex organs in males. In a dose of 60 mg/kg adiphenine produced a significant decrease (compared with the control) in weight of the ventral prostate in males and also in the weight of the ovaries and uterus in the females (weight of ovaries and uterus 43 and 160 mg respectively in the control and 30 and 101 mg in the experimental series).

The results of experiments to study the effect of adiphenine on estrous function of rats with a normal 4-5 day cycle showed depression of the estrous reaction of the rats by the drug. In a dose of 50 mg/kg given for 20 days, adiphenine increased the mean duration of the estrous cycle from 5 ±0.6 days in the control to 11.7 ±2.1 days in the experimental series. The total number of days in the phase of estrus was 33.6% of the total number of observations in the control and only 20% in the experimental animals receiving adiphenine in a dose of 50 mg/ kg body weight. In a dose of 25 mg/ kg, adiphenine had a more marked inhibitory action on the estrous cycle of the rats.

Tests of the pituitary of adult female rats for total gonadotropin content revealed no significant difference in gonadotropin level between the experimental and control animals. Gonadotropic activity of the

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TABLE 1. Content of Follicle-Stimulating Hormone in Pituitary of Female Rats Determined by the Steelman–Pohley Method [6]

Substance administered	Mean wt. of ovaries (in mg/100 g body wt.)	Content of hormone		
		in 1 mg of ovary	P	%
Control: HCG 40 units	21,0± 1,4			
HCG + suspension of pituitaries of rats receiving distilled water for 20 days	86,0± 1,7 190± 1,4	104± 1,6		100
Adiphenine 10 mg/kg	244± 4,0	158± 4,2	<0,01	152
» 20 »	235± 10,0	150± 10,2	<0,05	144
» 40 »	214± 4,0	128± 4,2	<0,005	122
» 60 »	200± 6,0	114± 6,2	>0,05	107
» 80 »	167± 1,5	87± 3,0	<0,05	83

Note. Tests were carried out on sexually immature female rats treated with chorionic gonadotropin (HCG) in dose of 40 units per rat (6.5 units per rat twice daily for 3 days). Suspension of pituitaries of experimental male rats receiving adiphenine was injected 3 times in the course of 3 days subcutaneously into sexually immature female rats (weight 45-50 g) in a dose equivalent to 2.5 pituitaries per rat.

TABLE 2. Content of Luteinizing Hormone in Pituitaries of Female Rats Determined by Method of Bell et al. [5]

Substance administered	No. of rats	Total cholesterol (in μg/100 mg ovary)	P
Suspension of pituitaries of rats receiving physiological saline for 20 days	7	2 300± 200	
Adiphenine 10 mg/kg	5	690± 30	
» 20 »	5	660± 70	>0,05
» 30 »	5	820± 120	>0,05
» 40 »	5	880± 60	<0,05
» 60 »	5	920± 35	<0,01
	5	1 200± 85	<0,01

Note. Tests carried out on sexually immature female rats (weight 45-50 g) prepared by preliminary injection of serum gonadotropin (50 units per rat) followed 72 h later by chorionic gonadotropin (25 units per rat). Suspension of pituitaries of experimental animals injected once intraperitoneally into sexually immature female rats on 11th day after injection of chorionic gonadotropin in dose equivalent to 1 pituitary per rat. Inhibition of luteinizing activity of pituitaries of female rats treated with adiphenine indicated by an increase in total cholesterol content in their ovaries compared with animals receiving physiological saline.

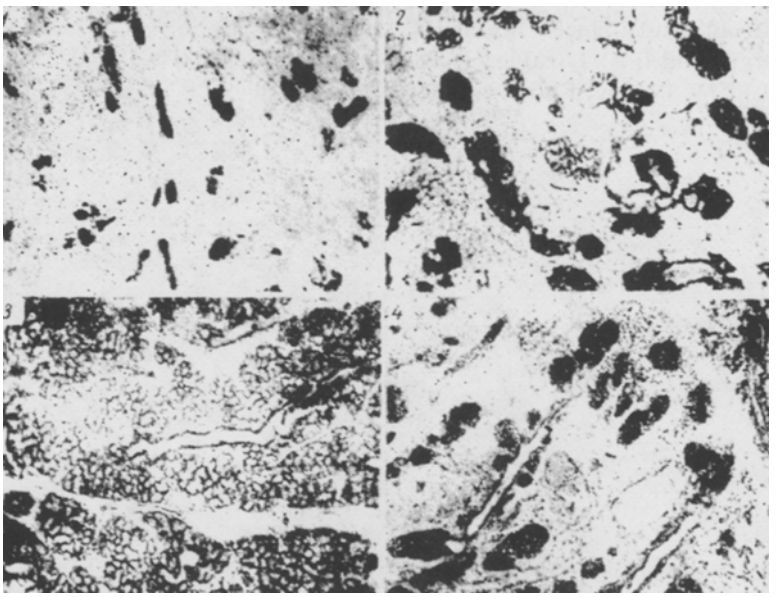

Fig. 1. Photomicrograph. Histological structure of rat mammary gland. 1) Control: a few undeveloped alveoli present, narrow lumen of lactiferous ducts; 2) after injection of estradiol monobenzoate (10 μg, 4 days): some widening of ducts of mammary gland and slight proliferation of alveolar-lobular tissue; 3) after injection of estradiol monobenzoate (10 μg, 4 days) together with chlorpromazine (15 mg/kg, twice daily for ten days): marked alveolar-lobular hyperplasia of mammary gland; 4) after injection of estradiol monobenzoate (10 μg, 4 days), chlorpromazine (15 mg/kg twice daily), and adiphenine (30 mg/kg twice daily, 10 days): marked decrease in proliferation and secretion of glandular epithelium of mammary gland compared with histological picture in Fig. 1, 3. Magnification 50 ×.

pituitaries was judged from changes in weight of the ovaries and uterus of infantile female rats (weight 45-50 g) receiving a subcutaneous injection of a suspension of pituitaries from experimental adult female rats.

Under the influence of adiphenine in a dose of 10-60 mg/kg the content of follicle-stimulating hormone in the male pituitaries was appreciably increased (Table 1).

The luteinizing activity of the pituitary of female rats (weight 150-180 g) was inhibited by adiphenine (Table 2).

The results of a study of histological sections of the mammary glands of adult female rats showed that adiphenine in a dose of 60 mg/kg (period of administration 10 days) diminished proliferation and secretion of the mammary glands caused by administration of estrogens both alone and together with chlorpromazine (Fig. 1).

With an increase in dose of adiphenine to 80 mg/kg given to estrogenized rats under the same conditions the drug showed no inhibitory effect on growth of the mammary gland and secretion evoked by administration of chlorpromazine, but on the contrary adiphenine potentiated the action of chlorpromazine, thereby manifesting its similarity to the action of the m-cholinolytic drug methyldiazine.

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