PHARMACOLOGICAL STUDY OF ADENERGIC MECHANISMS OF COMPENSATORY HYPERTROPHY OF THE OVARY

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Hemicastrated female rats were given daily injections of diethylstilbestrol propionate (DESP) or oil for 1 week, together with one of the following substances: propranolol hydrochloride, pyrroxan, dihydroergotoxin, chlorpromazine, α-methyldopa, disulfiram, L-dopa, and phenytoin sodium. The adrenoblockers, and also chlorpromazine and α-methyldopa, depressed the compensatory hypertrophy of the ovary (CHO) and prevented the effect of estrogen inhibiting CHO, whereas the dopamine-β-hydroxylase inhibitor disulfiram potentiated the effect of DESP. In small doses, L-dopa stimulated CHO but in large doses, like phenytoin sodium, although not affecting CHO it potentiated the inhibitory action of the estrogen. It is postulated that the key role in the mechanism of CHO is played by noradrenalin liberation in central adrenergic neurons, whereas the action of estrogens inhibiting secretion of follicle-stimulating hormone is mediated through stimulation of dopamine release.

KEY WORDS: adrenergic agents; compensatory hypertrophy of the ovary; estrogens.

Date on the role of biogenic amines in the liberation of hypothalamic gonadotropin releasing factors (RF) are extremely contradictory. On the one hand, McCann and co-workers [13, 16] showed that noradrenalin and dopamine determine the discharge of RF which stimulate secretion of follicle-stimulating and luteinizing hormones (FSH-RF and LH-RF, respectively) from the median eminence of the hypothalamus. On the other hand, several workers consider that dopamine inhibits gonadotropin secretion [8, 9, 11, 14]. Data on the effect of estrogens on the catecholamine level in the hypothalamus [4, 6, 7] are also contradictory, which makes the mechanism of the inhibitory action of estrogens on pituitary gonadotropic function difficult to understand. Yet the problem itself is of fundamental importance, for observations suggest that a key role in the realization of the age program of development and aging and of associated pathology is played by an increase in the threshold of sensitivity of the hypothalamus to homeostatic inhibition [2]; in the reproductive system this is reflected in an age decrease in the sensitivity of the hypothalamic-gonadotropic system to the inhibitory action of estrogens [1].

Data on the effect of substances acting on metabolism or catecholamine liberation, on the gonadotropic function of the pituitary, and on the sensitivity of the hypothalamic-gonadotropic system to the inhibitory action of estrogens are described in this paper.

EXPERIMENTAL METHOD

Experiments were carried out on 479 female albino rats aged 3-4 months. Hemicastration was performed on all the animals and, starting on the day of the operation and for 7 days they received daily subcutaneous injection of 0.1 ml vegetable oil or 0.57 μg diethylstilbestrol propionate (DESP) and one of the following substances (the daily doses are shown):

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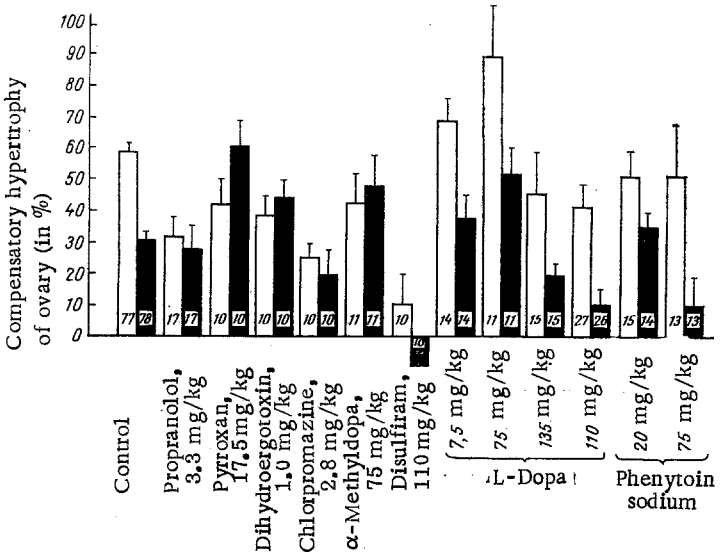

Fig. 1. Effect of adrenergic drugs on CHO and inhibitory action of diethylstilbestrol. Unshaded columns) injection of oil; shaded columns) injection of diethylstilbestrol. Numbers in columns show numbers of animals in groups. Values given are M ± m.

propranolol hydrochloride (3.3 mg/kg, intraperitoneally), pyrroxan (a central α-adrenoblocker [3], 17.5 mg/kg, intraperitonally), dihydroergotoxin (1 mg/kg, subcutaneously), chlorpromazine (2.8 mg/kg, intraperitoneally), α-methyldopa(75 mg/kg, by mouth), disulfiram (110 mg/kg, by mouth), L-dopa (7.5 and 110 mg/kg, intraperitonally; 75 and 135 mg/kg, by mouth) and phenytoin sodium (20 mg/kg, by mouth; 75 mg/kg intraperitoneally). On the eighth day after hemicastration the animals were killed and the degree of compensatory hypertrophy of the ovary (CHO) was determined.

EXPERIMENTAL RESULTS AND DISCUSSION

As Fig. 1 shows, the adrenolytics inhibited CHO induced by hemicastration. Administration of the adrenoblockers and also chlorpromazine and α-methyldopa prevented the action of the estrogen in inhibiting CHO, whereas disulfiram potentiated the effect of DESP. L-Dopa, in doses of 7.5 and 75 mg/kg stimulated CHO; a further increase in the dose did not lead to changes in CHO compared with the control. Meanwhile, in large doses, L-dopa potentiated the inhibitory action of estrogens on CHO. Phenytoin sodium had no effect on CHO and in a high dose it potentiated the inhibitory action of DESP.

It is well known that CHO in hemicastrated rats is due to increased activity of the hypothalamic-gonadotropic system in response to a fall in the estrogen level in the body [5, 15, 17]. The results of the present experiments are in agreement with the view of the mediator role of catecholamines in the mechanisms of FSH release. Inhibition of the synthesis or secretion of catecholamines or blocking the adrenoceptors inhibits CHO. Experiments with disulfiram, which selectively blocks dopamine-β-hydroxylase [10], lead to the conclusion that the liberation of FSH-RF is determined by noradrenalin and not by dopamine. The results are in agreement with observations by Zolovick [18] who showed that 6-hydroxydopamine blocks CHO by reducing the noradrenalin content in the hypothalamus, and they also agree with the results of experiments *in vivo* and *in vitro* in which dopamine inhibited FSH secretion [8, 9, 11, 14]. The fact that in the present experiments injection of L-dopa in small doses stimulated CHO, but in large doses it had no effect or actually inhibited CHO slightly, suggests that in large doses L-dopa either inhibits noradrenalin synthesis or that parallel with the increase in noradrenalin synthesis there is an increase under the influence of L-dopa in the synthesis and secretion of dopamine, which has the opposite action on the liberation of FSH-RF.

Data on the blocking action of chlopromazine, α-methyldopa, and adrenoblockers on the inhibitory effect of estrogens on CHO points to the participation of catecholamines in mediation of the inhibitory action of estrogens on gonadotropin secretion. There is reason to

suppose that estrogens exert their inhibitory action on gonadotropin secretion by inhibiting the synthesis or activity of dopamine-β-hydroxylase. This hypothesis is confirmed by findings showing an increase in noradrenalin synthesis in castrated animals and that estrogens inhibit this process [4, 6] and also that the liberation of dopamine is increased in terminals of dopaminergic neurons of the median eminence of the hypothalamus after administration of estrogens [8, 9]. The results now obtained, showing that disulfiram potentiates the effect of DESP, indicate a role for dopamine as the mediator for the action of estrogens on FSH-RF secretion and, correspondingly, on FSH secretion by a mechanism of negative feedback. This same mechanism possibly participates in the potentiation of the action of estrogens on CHO following administration of large doses of L-dopa or phenytoin sodium, which facilitate dopamine release in the brain [12].

Several facts thus indicate that a key role in the mechanism of CHO due to secretion of FSH-RF and FSH is played by the liberation of noradrenalin in central adrenergic neurons, whereas the action of estrogens in inhibiting FSH secretion is mediated through stimulation of dopamine release. This mechanism could be explained by the repressor action of estrogens on the synthesis or activity of dopamine-β-hydroxylases, although further study of this problem is required.

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