INCREASED HYPOTHALAMIC SENSITIVITY TO ESTROGEN INHIBITION INDUCED BY L-DOPA, PHENYTOIN, EPITHALAMIN, AND PHENFORMIN IN OLD RATS

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UDC 612.826.4.014.46 : 615.256.51] : 612.67

Daily administration of 0.57 μg diethylstilbestrol propionate (DESP) to hemicastrated rats inhibited by 48% compensatory hypertrophy of the ovary (CHO) in 3-month-old animals but by only 3% in 18-month-old rats. After injection of phenytoin, L-dopa, epithalamin, or phenformin concurrently with this same dose of DESP into old rats, inhibition of CHO amounted to 65-98%. L-Dopa and epithalamin produced the same effect when injected into the third ventricle. The results of these experiments indicate the functional nature of the age changes in hypothalamic sensitivity to estrogens.

KEY WORDS: hypothalamus; age sensitivity; estrogens; compensatory hypertrophy of the ovary.

An increase in the threshold of hypothalamic sensitivity to inhibition in the reproductive, energy-producing, and adaptive systems with age has been shown previously [3, 5-7]. A number of external factors capable of inducing or intensifying age changes and, in particular, certain carcinogens [2, 4] also raise the threshold of hypothalamic sensitivity. It thus becomes necessary to look for substances that could increase the sensitivity of the hypothalamus to regulatory factors. Besides the practical importance of such substances, their effect could extend our ideas on the actual mechanism of the increase in the threshold of hypothalamic sensitivity.

EXPERIMENTAL METHOD

Experiments were carried out on 484 female albino rats. The left ovary was removed from the animals at the age of 17-19 months and, starting from the day of operation, once a day for 7 days a subcutaneous injection was given of 0.57 μg diethylstilbestrol propionate (DESP) or 0.1 ml vegetable oil, together with an injection of one of the following substances: L-dopa (20 mg, intraperitoneally), phenytoin (22.5 mg by mouth), reserpine (0.03 mg, intraperitoneally), phenformin (5 mg, by mouth), and epithalamin (an acetic acid extract of bovine pineal glands, 2 mg, subcutaneously). Young (3 months) female rats served as an additional control. In a special series of experiments L-dopa (10 μg) and epithalamin (25 μg) were injected into the third ventricle through stereotaxically inserted cannulas. Control animals received an injection of 5 μl physiological saline through cannulas. On the eighth day after hemicastration the animals were decapitated and the degree of compensatory hypertrophy of the ovary (CHO) was determined.

EXPERIMENTAL RESULTS AND DISCUSSION

The dose of DESP sharply inhibiting CHO in 3-month-old rats was ineffective in old animals (Table 1). These observations agree with others in which the dose of estrogen which completely inhibited CHO in 18-

Laboratory of Endocrinology, N. N. Petrov Research Institute of Oncology, Ministry of Health of the USSR, Leningrad. (Presented by Academician V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 80, No. 11, pp. 96-98, November, 1975. Original article submitted February 18, 1975.

TABLE 1. Effect of Various Pharmacological Agents on Inhibition of CHO by Diethylstilbestrol Propionate

Conditions	Injection of estrogen	No. of rats	Weight of left ovary (in mg)	Weight of right ovary (in mg)	CHO (right) in %
Control	—	77	26,3±0,8	40,1±1,2*	59,0±3,2
3-month-old rats	+	78	28,3±1,0	34,6±0,8*	31,0±3,4†
17-19-month-old rats	—	31	45,8±1,7	53,5±2,2*	22,6±6,5
	+	34	41,6±1,8	47,2±2,4*	21,9±8,2
L-Dopa	—	12	43,1±3,5	57,9±3,6*	33,8±5,5
	+	14	46,1±2,7	45,6±2,7	4,7±8,4†
Phenytoin	—	25	47,8±1,7	54,6±1,9*	19,4±4,4
	+	30	49,4±1,9	51,7±2,2	6,8±4,3†
Epithalamin	—	20	48,8±2,3	59,1±4,1*	22,5±7,2
	+	20	46,2±3,5	40,9±2,5	0,4±7,0†
Phenformin	—	20	50,1±3,1	52,4±3,8	7,3±4,6‡
	+	19	54,2±3,4	54,4±4,5	1,7±4,2
Reserpine	—	15	47,6±2,5	47,1±3,9	—0,5±5,0‡
	+	15	46,7±2,3	41,0±2,3	—8,9±5,3

* Difference from figure for left ovary significant ($P < 0.05$).

† Difference from corresponding figure for rats of the same group, but not receiving estrogen, significant ($P < 0.05$).

‡ Difference from corresponding figure for old control rats significant ($P < 0.05$).

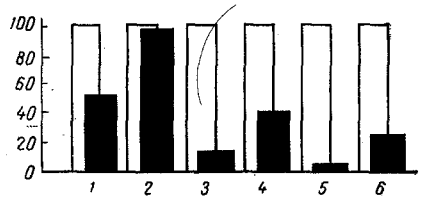

Fig. 1

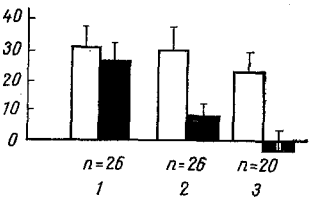

Fig. 2

Fig. 1. Effect of drugs on ability of estrogen to inhibit CHO in old rats: 1) control (3 months); 2) control (17-19 months); 3) L-dopa; 4) phenytoin; 5) epithalamin; 6) phenformin. Unshaded columns – no estrogen given; shaded columns – DESP given. Here and in Fig. 2, ordinate – degree of CHO (in %). In each group the value of CHO in rats not receiving estrogen is taken as 100%.

Fig. 2. Inhibition of CHO by estrogens in old rats after injection of L-dopa and epithalamin into third ventricle: 1) control (5 μl physiological saline); 2) L-dopa; 3) epithalamin. Unshaded columns – no estrogen given; shaded columns – DESP given.

month-old rats was much greater than the corresponding dose for young animals [3]. L-Dopa, phenytoin, and epithalamin, although not affecting CHO, significantly increased the sensitivity of the hypothalamic-pituitary system to the inhibitory action of the estrogen (Fig. 1). Phenformin inhibited, whereas reserpine completely prevented, CHO.

The increase in the threshold of hypothalamic sensitivity to homeostatic factors probably plays the key role both in the carrying out of the internal neuroendocrine program of development of the organism and in adaptation to the action of many external factors. Several observations, especially normalization by pineal extracts [1, 3, 8] of hypothalamic sensitivity to estrogens and prednisolone, have shown that the increase in the level of sensitivity is based on functional changes.

The most interesting fact was that preparations with different mechanisms of action had identical effects. L-Dopa most probably exerts its effect by increasing the catecholamine level in the hypothalamus. This view is supported by data showing a fall in the catecholamine level in the hypothalamus during aging [9, 11] and possible restoration of the estrous cycle in old rats by administration of L-dopa and noradrenalin [15]. The mechanism of action of the other drugs on hypothalamic sensitivity to estrogens remains un-

explained. Presumably phenytoin exerts its action through its effect on the potassium "pump" [10]. The direct action of phenytoin on catecholamine metabolism is another possibility [13]. Data on the direct effect of L-dopa and epithalamin on the hypothalamus agree with the results of the present experiments in which these drugs were injected into the third ventricle (Fig. 2). The action of phenformin (an antidiabetic biguanidine preparation) can be linked with the improvement in carbohydrate metabolism in the body as a whole and, probably, in the glial cells of the brain with their role in neuronal nutrition [14]. The antigonadotropic action of phenformin also reflects two-way connections between energy and reproductive homeostasis in the body, a conclusion supported by data on metabolic changes after castration, on the one hand, and the connection between body weight and the function of the reproductive system on the other hand [12].

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