ROLE OF PERIPHERAL CATECHOLAMINE MECHANISMS IN CENTRAL ACTIVATION OF THE HYPOPHYSEO-ADRENOCORTICAL SYSTEM INDUCED BY RESERPINE

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Inhibition of the function of the peripheral divisions of the sympathico-adrenal system prevents the manifestations of stimulation of the hypophyseo-adrenocortical system by the action of reserpine.

In doses exceeding 0.25 mg/kg, reserpine induces increased activity of the hypophyseo-adrenocortical system (HAS) in animals [4]. Special attention has been paid to the effect of reserpine on the central nervous resources of biogenic amines: their liberation and subsequent exhaustion as factors responsible for changes in the neurochemical structure of intracerebral, and primarily hypothalamo-hypophyseal, interrelationships [5, 6-8].

Meanwhile exhaustion of the central nervous resources of noradrenalin increases adrenomedullary activity, with an increase in the secretion and synthesis of the hormone [2], and it is accompanied also by an increase in tyrosine hydroxylase activity in the adreanal medulla and the superior cervical sympathetic ganglion [13]. On the basis of these observations, and also of the concept of reciprocity between individual components of the sympathico-adrenal system [2, 3], in the present investigation it was decided to study the possible role of peripheral catecholamine mechanisms in the production of the central HAS-activating effect of reserpine. Data in the literature concerning the role of these mechanisms in the regulation of adrenocorticotropic function of the pituitary are contradictory [1, 9].

Bearing in mind reports that the effect is still present after demedullation of the adrenals [11], the ability of reserpine to strengthen adrenocortical function was investigated against the background of procedures blocking peripheral adrenergic activity at different levels (ganglionic, neuronal, receptor).

EXPERIMENTAL METHOD

Experiments were carried out on 200 albino rats of both sexes weighing 160-250 g. The following preparations were used: reserpine ("Rausedil"), dihydroergotoxin, dibenamine (N,N-dibenzyl-β-chloroethylamine hydrochloride), hexamethonium (1,6-hexamethylene-bis-trimethylammonium iodide), piriline (1,2,2,6,6-pentamethyl-piperidine paratoluenesulfonate), bretylium (N-orthobromobenzyl-N-ethyl-N,N-dimethylammonium bromide), and chlorpromazine (10,3'-dimethylaminopropyl-2-chlorophenothiazine); the doses, times, and methods of administration are shown in the tables. Separate experiments were carried out on demedullated animals. Demedullation of the adrenals was performed by crushing the medulla through an incision in the capsule and cortex. Completeness of demedullation was verified on the 10th-12th day after the operation. By studying the excretion of catecholamines in the urine (in animals undergoing the

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TABLE 1. Concentration of 11-HCS in Blood Plasma and of AA in Adrenals of Albino Rats after Administration of Reserpine Compared with Changes after Administration of ACTH, Stress, Adrenalectomy, and Demedullation of Adrenals ($\bar{X} \pm \bar{S}x$)

Group No.	Procedure	Dose, time, mode of administration	11-HCS (in μg%)	n	AA (in mg/100 g)	n
1	Intact animals	–	31 ± 0.53	19	372 ± 12	18
2	ACTH	50 units/100 g subcutaneously after 40 min	60 ± 12[2]	4	287 ± 15[2]	7
3	Stress	Swimming in water at a temperature of 16-18° for 15-20 min	105 ± 2.3[1]	13	249 ± 15[1]	8
4	Adrenalectomy	7-8 days after operation	5.9 ± 1.7[1]	12	–	–
5	Demedullation	10 days after operation	26 ± 5.4	18	–	–
6	Demedullation + ACTH	As in lines 2 and 5	76 ± 12[1]	3	–	–
7	Reserpine	1 mg/kg subcutaneously, after 2 h	80 ± 2.3[1]	12	269 ± 14[1]	8
8	"	1 mg/kg subcutaneously, after 24 h	62 ± 4.0[1,3]	10	312 ± 10[2]	4
9	"	1 mg/kg subcutaneously, after 48 h	34 ± 6.2	4	384 ± 12	4
10	"	0.5 mg/kg intraperitoneally after 2 h	48 ± 3.2[1]	4	–	–

[1]Compared with group 1, $P < 0.001$.
[2]Compared with group 1, $P < 0.05$.
[3]Compared with group 7, $P < 0.01$.

the mock operation: adrenalin, 0.17 ± 0.002 μg/day, noradrenalin 0.35 ± 0.02 μg/day; for the demedullated animals: adrenalin 0.015 ± 0.01 μg/day, noradrenalin 0.70 ± 0.17 μg/day) and from the content of catecholamines in the residual adrenal tissues (the content of catecholamines did not exceed 1/40 of normal). Catecholamines were determined by the trihydroxyindole method [3]. The ability of the demedullated animals to intensify their adrenocortical function was tested by their response to ACTH. HAS activity was estimated by determination of the 11-hydroxycorticosteroids (11-HCS) in the blood plasma and ascorbic acid (AA) in the adrenals.

EXPERIMENTAL RESULTS AND DISCUSSION

The data in Table 1 demonstrate the changes in adrenocortical activity after administration of reserpine and also, for comparison, after certain other procedures (stress, ACTH) which stimulate adrenocortical function. A marked increase in the 11-HCS level was observed 2 h after administration of reserpine in a dose of 1 mg/kg. This increase was smaller 24 h after injection, and after 48 h no increase in 11-HCS could be found. These findings corresponded closely to the dynamics of the changes (a decrease and subsequent return to normal) of the AA concentration in the adrenals.

The results of estimation of 11-HCS and ascorbic acid following administration of reserpine against the background of procedures preventing activation of the hormonal and mediator components of the sympathico-adrenal system are shown in Table 2. Administration of dibenamine and dihydroergotoxin completely prevented the increase in 11-HCS concentration induced by reserpine. The 11-HCS concentration remained at the level characteristic of the effects of the adrenergic blocking agents themselves: slightly increased after injection of dihydroergotoxin and substantially reduced under the influence of dibenamine. A well-marked but incomplete prevention of the reserpine effect was observed against the background of hexamethonium and piriline. Bretylium and adrenodemedullation prevented activation of HAS to a lesser degree, but a combination of these factors completely prevented the increase in the 11-HCS level produced by reserpine. Against the background of chloropromazine the action of reserpine on the AA content in the adrenals was unchanged, but the 11-HCS level in the blood was actually higher than after reserpine alone had been given because chlorpromazine itself considerably raised the 11-HCS concentration.

The most important finding was the complete prevention of activation of the HAS by a combination of factors (obviously with a peripheral action) such as demedullation of the adrenals and blocking of the sympathetic endings by bretylium. The absence of this effect following demedullation and

TABLE 2. Effect of Blocking of the Sympathico-Adrenal System at Different Levels on Effect of Reserpine on Hypothalamo-Hypophyseo-Adrenal System of Rats ($\bar{X} \pm S\bar{x}$)

Group No.	Procedure	n	Dose, time, mode of administration	11-HCS in blood plasma (in μg%)	AA in adrenals (in mg/100 g)
1	Intact animals	20	—	30 ± 0.61	487 ± 12
2	Reserpine	29	1 mg/kg subcutaneously, after 2 h	85 ± 1.4[1]	291 ± 10[1]
3	Dibenamine	12	15 mg/kg subcutaneously, after 24 h	20 ± 2.7[1]	—
4	Dibenamine + reserpine	5	As in lines 2 and 3	22 ± 3.9[2,3]	—
5	Dihydroergotoxin	3	1 mg/kg intraperitoneally, after 2 h 10 min, second injection 40 min later	40 ± 6.4	—
6	Dihydroergotoxin + reserpine	7	As in lines 2 and 5	38 ± 6.1	—
7	Hexamethonium	3	10 mg/kg intraperitoneally, after 2 h 30 min	41 ± 5.5	—
8	Hexamethonium + reserpine	6	As in lines 2 and 7	54 ± 6.9[1,3]	—
9	Piriline	3	10 mg/kg intraperitoneally, after 2 h 30 min	32 ± 2.7	454 ± 21
10	Piriline + reserpine	6	As in lines 2 and 9	57 ± 7.2[1,3]	392 ± 17[1,3]
11	Bretylium	6	30 mg/kg intraperitoneally, after 2 h 30 min	35 ± 8.9	472 ± 17
12	Bretylium + reserpine	9	As in lines 2 and 11	61 ± 9.2[1,3]	317 ± 11[1]
13	Demedullation of Adrenals	18	After 10 days	26 ± 5.4	—
14	Demedullation + reserpine	3	As in lines 2 and 13	59 ± 4.4[1,3]	—
15	Demedullation + bretylium	3	" " " 11 and 13	19.5 ± 3.5[1]	—
16	Demedullation + bretylium + reserpine	6	" " " 2, 11, and 13	25 ± 6.4[3]	—
17	Chlorpromazine	3	2 mg/kg subcutaneously, after 2 h 30 min	63 ± 9[1]	—
18	Chlorpromazine + reserpine	5	As in lines 2 and 18	94 ± 3.4[1,4]	293 ± 8[1]

[1]Compared with value in intact rats, $P < 0.001$.
[2]The same, $P < 0.05$.
[3]Compared with value in reserpinized rats, $P < 0.001$.
[4]The same, $P < 0.05$.

administration of bretylium separately may indicate a role of the hormonal and mediator components of the sympathico-adrenal system as alternative pathways for the mechanism of the HAS-activating effect of reserpine. This combination was just as effective as dibenamine, i.e., α-receptor blocking of both hormonal and mediator effects of the catecholamines.

These results do not contradict existing views regarding the role of the central effects of reserpine in HAS activation. However, whereas exhaustion of the resources of biogenic amines in the brain may be the trigger mechanism of HAS activation, peripheral adrenergic mechanisms probably act as the pathways for realization of this effect or, at least as factors necessary for this effect to be produced.

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