EFFECT OF SOME HYPOTENSIVE DRUGS ON LIBERATION AND DEPOSITION OF PRESSOR AMINES

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In recent years the role of the pressor amines (adrenalin and noradrenalin) in the pathogenesis of essential hypertension, angina pectoris, and other diseases associated with disturbance of vascular tone has been established [2, 17]. The work of Soviet and other investigators has shown that the action of certain hypotensive drugs is due to their interference in the processes of synthesis, deposition, liberation, and inactivation of catecholamines in adrenergic structures [1, 5, 8, 18].

Reserpine is known to lower the concentration of catecholamines in various tissues [15, 18]. This effect is due to two factors: their influence on the central nervous system [7] and their direct action on the peripheral tissue depots of these amines [16]. The question of which influence is predominant is a matter for debate. According to the observations of Stitzel and co-workers [20], the action of a single dose of reserpine on the adrenals is the result of stimulation of the central nervous system; so far as the effect of reserpine on the catecholamines depot in the heart muscle is concerned, its direct peripheral action is predominant. This corresponds to the transformation of noradrenalin from the bound into the free form, followed by its deamination with monoamine oxidase (MAO) [8, 18].

In connection with the foregoing facts it was interesting to investigate the effect of ganglion-blocking agents, sympatholytic drugs and monoamine oxidase inhibitors (as the nonhydrazine series), used as hypotensive drugs on the liberation and deposition of catecholamines in organs receiving a sympathetic nerve supply, and on the action of reserpine in "exhausting" the catecholamines in the heart muscle and adrenals.

To give further information on the ability of these substances to influence the liberation of noradrenalin from sympathetic nerve endings, experiments were carried out on adrenalectomized cats and on cats with intact adrenals in which a pressor effect appeared on administration of the ganglion stimulator dimethylphenylpiperazine iodide (DMPP).

EXPERIMENTAL METHOD

Experiments were carried out on rats of both sexes weighing 150-200 g. Catecholamines were determined in the heart muscle and adrenals by V. O. Osinskaya's fluorescence-analysis method with slight modifications [4, 14]. The total content of catecholamines in the heart muscle was expressed in μg adrenalin base per gram fresh tissue, and the content of adrenalin in the adrenals in μg adrenalin base per weight of 2 adrenals, reflecting the content of adrenalin in the medulla more accurately. The rats took part in the experiment at various intervals of time after administration of the preparations. Adrenalectomy was carried out on cats intraperitoneally under urethane–chloralose anesthesia. The blood pressure was recorded with a mercury manometer by the usual method.

Reserpine (2 mg/kg intramuscularly) was injected 16-18 h before decapitation of the rats, pyrilene (1, 2, 2, 6, 6,-pentamethylpiperidine toluenesulfonate; 350 mg/kg) 3 h before the experiment, ornid (orthobromobenzyl-N,N-dimethyl-N-ethylammonium bromide; 50 mg/kg intraperitoneally) 1 h before the experiment, and MAOI inhibitor (MAOI) from the group of propinylamine derivatives, conventionally named OCP (N-orthochlorobenzyl-N-methyl-2-propinylamine hydrochloride; 100 mg/kg), 15-16 h before the experiment. In the case of combined administration of reserpine and the above-mentioned preparations, the following scheme of administration was used: pyrilene (350 mg/kg subcutaneously) was given once 1 h before injection of reserpine in a dose of 2 mg/kg, ornid (30, 20, and 20 mg/kg intraperitoneally) was

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TABLE 1. Effect of Pyrilene, Ornid, and OCP on Concentration of Catecholamines in Heart Muscle and of Adrenalin in Adrenals of Rats (M ± m)

Preparation	Dose (in mg/kg) and time (in hours after injection of preparation	Total concentration of catecholamines in myocardium (in μg noradrenalin/g fresh tissue)	Concentration of adrenalin in adrenals (in μg adrenalin per wt. of 2 adrenals)
Control	–	1.73 ± 0.024 n = 24	13.57 ± 1.0 n = 16
Pyrilene	350; 3	2.77 ± 0.125 n = 13	21.03 ± 1.62 n = 12
Ornid	50; 1	1.86 ± 0.09 n = 9	9.19 ± 0.33 n = 9
OCP	100; 15-16	2.03 ± 1 n = 8	

Legend: here and in Table 2, n represents number of experiments.

TABLE 2. Effect of Preliminary Injection of Pyrilene, Ornid, and OCP on Concentration of Catecholamines in Myocardium and of Adrenalin in Adrenals of Reserpinized Rats (M ± m)

Preparation	Total concentration of catecholamines in heart muscle (in μg noradrenalin/g fresh tissue)	Concentration of adrenalin in adrenals (in μg noradrenalin per weight of two adrenals)
Control	1.73 ± 0.024 n = 24	13.57 ± 1.0 n = 16
Reserpine	0.71 ± 0.057 n = 9	6.14 ± 0.67 n = 9
Reserpine + pyrilene	1.17 ± 0.04 n = 7	7.55 ± 0.7 n = 7
Reserpine + ornid	1.19 ± 0.04 n = 9	6.72 ± 0.72 n = 9
Reserpine + OCP	1.16 ± 0.03 n = 7	–

given 1 h before injection of reserpine, 6 h after the first injection, and 1 h before decapitation, and OCP (100 mg/kg intramuscularly) was given 2-3 h before injection of reserpine.

The doses and time intervals after injection of the preparations were chosen on the basis of data in the literature and results obtained by the authors in preliminary experiments.

EXPERIMENTAL RESULTS AND DISCUSSION

Pyrilene, 3 h after injection, and OCP, 16 h after injection increased the content of catecholamines in the heart muscle of intact rats, and the adrenalin content in the adrenals was also increased by pyrilene. One hour after injection of ornid no changes were observed in the content of catecholamines in the heart muscle, while the adrenalin level in the adrenals had fallen ($P < 0.05$). The results are summarized in Table 1.

From 16 to 18 h after injection of reserpine in a dose of 2 mg/kg a marked decrease in the total concentration of catecholamines in the heart muscle and of adrenalin in the adrenals was observed. Preliminary injection of the test substances by the scheme described above did not completely prevent, but considerably inhibited, the development of the exhaustive action of reserpine on the catecholamine depot in the heart muscle. Administration of ornid did not change the action of reserpine on the adrenalin reserves in the adrenal medulla, but pyrilene showed a tendency to inhibit the reserpine effect.

The results of this series of experiments are given in Table 2. Intravenous injection of DMPP is known to be accompanied by a pressor reaction due to two factors: release of adrenalin from the adrenals and liberation of mediators (mainly noradrenalin) from depots located in the sympathetic nerve endings [9]. The influence of the first factor was eliminated in the adrenalectomized animals. Substances influencing liberation of noradrenalin from the nerve endings naturally modified to some extent the reaction to DMPP.

Ornid, in a dose of 10 mg/kg, given 1 h before injection of DMPP to intact animals, did not change or slightly increased the pressor reaction to DMPP. These results are in agreement with the observations of E. S. Rozovskaya [3]. In adrenalectomized cats the same dose of ornid 30 min and 1 and 2 h after injection completely or almost completely abolished the elevation of blood pressure in response to injection of DMPP, whereas adrenalectomy itself did not affect this reaction. In these same conditions the reaction to injection of noradrenalin persisted.

Similar results in adrenalectomized cats were also obtained after preliminary injection of the propinylamine derivative pargilin (50 mg/kg for 4 days, 5th injection 2 h before adrenalectomy).

It was found that the hypotensive drugs of different chemical structure and mechanism of action inhibited the "exhausting" action of reserpine on the catecholamine reserves in the heart muscle when injected simultaneously. At the same time, these drugs had no effect on the action of reserpine on the adrenal medulla. It may be supposed that the main role in the action of these substances on reserpine effects in relation to the catecholamine depot of the heart muscle is played not by removal of nervous influences (which may take place to some extent when ganglion-blocking drugs are used) but to their direct action on the reserves of pressor amines in the heart muscle. Because the effects of pyrilene, ornid, and MAOI on reserpinized cats have common features, it may be concluded that the mechanism of their action also possesses a common aspect – ability to inhibit liberation of mediator from sympathetic nerve endings. In the literature this action is called bretylium-like, because bretylium (the Western analogue of ornid) possesses antiguanethidene and antireserpine activity, while the sympatholytic action of bretylium (ornid) is regarded as the result of inhibition of liberation of mediator from sympathetic nerve endings [8]. So far as the effect of MAOI on this process is concerned, it can be considered that it is due to some extent also to blocking of the enzyme although, according to observations of Gessa and co-workers [10], MAOI possess bretylium-like action in doses which do not block MAO.

Confirmation of the above observations was obtained in experiments on adrenalectomized cats. Ornid and MAOI diminished or completely abolished the pressor reaction to DMPP, demonstrating their ability to influence the liberation of neurohormones from sympathetic nerve endings.

It has also been shown that pyrilene and ornid differ in their effects on the catecholamine depot in the myocardium of intact animals. The reason for this is evidently that gangliolytics inhibit liberation of labeled noradrenalin from the rat's heart [12] and intensify its absorption in depots [6], whereas bretylium (ornid) inhibits both processes [13]. Probably for this reason the total content of catecholamines in the myocardium remains unchanged after a single injection of ornid. These findings are in agreement with the results of work by Trinus [4] on the rabbit's aorta. In contrast to ganglion-blocking drugs (pyrilene), ornid does not inhibit the chromaffin tissue of the adrenals, as a result of which it evidently reduces the reserves of adrenalin in the medulla. The primary pressor reaction after administration of bretylium (ornid) to certain species of animals may be associated with this phenomenon [11]. This suggestion is confirmed by the fact that in cats with intact adrenals ornid does not block the reaction to DMPP, but may even intensify it slightly.

It may be concluded from these investigations that an important role in the hypotensive effect of drugs differing in their chemical structure and character of action – ornid, pyrilene, and OCP – is played by their ability to influence catecholamine metabolism by blocking liberation of mediators from sympathetic nerve endings. It is probable that this effect is important in the mechanism of the therapeutic antihypertensive action of these compounds.

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