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The effect of α-methyldopa on excretion of noradrenaline metabolites

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The effect of α-methyldopa on the rate of release of noradrenaline metabolites in patients with essential hypertension has been examined. The excretion of normetadrenaline increases during the first few hr after a dose of α-methyldopa while α-methylnormetadrenaline can be detected in the urine 8–12 hr after the initial dose. The results support the idea that α-methyldopa displaces noradrenaline from storage sites, the noradrenaline in turn being replaced by α-methylnoradrenaline.

THE blood pressure of hypertensive patients may be lowered by (−)-α-methyldopa (Oates, Gillespie & others, 1960; Sjoerdsma & Udenfriend, 1961). Suggestions that have been put forward to explain its action are: (1) that it blocks the synthesis of noradrenaline; (2) that it depletes body stores of noradrenaline; (3) that it replaces noradrenaline at its storage sites with α-methylnoradrenaline.

The first suggestion was made by Sourkes (1954), who showed that large amounts of α-methyldopa inhibited dopa decarboxylase. This prevented the formation of noradrenaline by blocking the penultimate stage in its synthesis. Gillespie, Oates & others (1962) and Pletscher (1963) suggested that α-methyldopa has a reserpine-like action and depletes body stores of noradrenaline. Day & Rand (1963) proposed the third mechanism. They suggested that α-methylnoradrenaline, which is formed from α-methyldopa (Carlsson & Lindqvist, 1962), displaced noradrenaline from its storage sites at sympathetic nerve endings. Once held at the nerve endings it acted as a "false transmitter substance". When the nerves were stimulated they released α-methylnoradrenaline instead of the true transmitter, noradrenaline, but since α-methylnoradrenaline had a much smaller pressor activity than noradrenaline, the blood pressure fell.

It seemed likely that some information might be obtained about the action of α-methyldopa by examining its effect on the rate of release of noradrenaline. The rate of noradrenaline secretion cannot be measured by a simple direct method but it can be measured indirectly by measuring the output of its metabolites in the urine. The most abundant of these is 4-hydroxy-3-methoxymandelic acid. Unfortunately, this metabolite is also a metabolite of adrenaline. We therefore measured normetadrenaline, the 3-*O*-methyl derivative of noradrenaline.

We now report the effect of α-methyldopa on the rate of excretion of normetadrenaline in patients with essential hypertension.

Methods

The method (Stott & Robinson, 1966) measures total normetadrenaline (i.e. free and conjugated) with an error of ±10%. Our results are not corrected for recovery, which ranged from 60–75%.

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The subjects were 10 patients (4 men, 6 women) with essential hypertension, kept in bed for the duration of the experiments. Their bladders were first emptied and the urine discarded. Then a control specimen of urine was collected over a period of 2 hr. The patients then took 500 mg of (±)-α-methyldopa by mouth and were told to drink liberally. Further urine specimens were collected at successive 2 hr intervals for 6 to 12 hr after the drug was given.

A similar experiment was made on one healthy normal subject, to whom 250 mg of (±)-α-methyldopa was given intravenously.

The normetadrenaline content of all the urine specimens was measured. Some of the specimens collected after the drug was taken were examined by two-dimensional paper chromatography for phenolic acids and amines (Robinson, Ratcliffe & Smith, 1959; Robinson & Smith, 1962).

Blood pressures were measured every 15 min throughout the experiments.

Results

The patients' output of normetadrenaline consistently rose in the first few hr after taking α-methyldopa. The output reached a peak between 4 and 6 hr and usually fell to the control values between 8 and 12 hr after they had taken the drug. α-Methylnormetadrenaline appeared in the urine 8–12 hr after the drug had been given, the level varying between 0·04–0·6% of the dose.

Fig. 1 shows the normetadrenaline output in μg/min of one patient. Table 1 gives normetadrenaline values before and at intervals after a dose of α-methyldopa.

The blood pressures of most of the patients fell slightly during the first hr and then rose to a peak between 1 and 1¾ hr after the drug was taken.

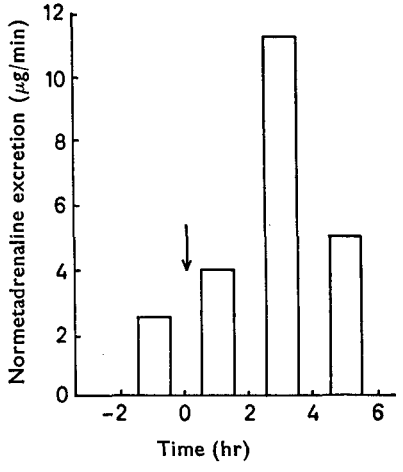

FIG. 1. Normetadrenaline excretion before and after taking 500 mg (±)-α-methyldopa. The drug was taken at the point marked by the arrow.

TABLE 1. NORMETADRENALINE VALUES (μG/MIN) BEFORE AND AFTER A DOSE OF α-METHYLDOPA

Patient No.	Before treatment	After treatment					
		2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	0·48	1·1	9·9	0·96	1·4	0·8	—
2	1·1	3·7	4·5	3·2	3·2	3·1	3·2
3	0·49	1·1	2·3	2·4	1·0	—	—
4	0·96	2·0	2·2	0·8	1·7	—	—
5	1·3	1·0	1·6	0·6	—	1·0	0·3
6	2·7	1·9	2·9	4·2	4·2	3·5	—
7	1·6	—	2·7	0·9	1·4	—	—
8	2·2	4·5	11·7	6·7	3·1	—	—
*9	5·3	6·3	5·8	4·4	4·2	—	—
*10	5·0	7·6	4·5	5·9	5·0	—	—
Normal subject	1·4	2·2	2·9	4·3	2·1	—	—

*Patients Nos 9 and 10 subsequently were shown to have phaeochromocytomas.

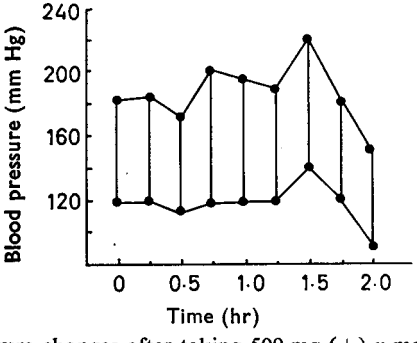

FIG. 2. Blood pressure changes after taking 500 mg (±)-α-methyldopa.

There was then a fall and 2 hr after the drug had been taken the blood pressures were lower than the control value (Fig. 2).

In the normal subject, the blood pressure did not change appreciably. Nevertheless, the output of normetadrenaline rose, reached a peak at 6 hr and then fell.

The output of phenolic acids was examined in one patient. The excretion of homovanillic acid fell strikingly. Two hr after taking the drug this metabolite formed about 50% of the control value and at 9 hr it was undetectable on the paper chromatogram. The urinary vanillic acid excretion was increased tenfold 9 hr after the patient had taken α-methyldopa.

Discussion

Our main finding was the rise in normetadrenaline excretion that occurred in the first few hr after α-methyldopa had been taken. If the main action of the drug is to inhibit dopa decarboxylase, a fall would have been expected rather than a rise. The finding that α-methyldopa causes an increased excretion of normetadrenaline could be explained in terms of a reserpine-like action. In addition, it is evident that the decarboxylation of dopa to dopamine was inhibited since the excretion of the dopamine metabolite, homovanillic acid, fell promptly and markedly.

It seems likely that this inhibition of the decarboxylation step is the result of substrate competition—the overwhelmingly greater amounts of α-methyldopa competing more successfully for the available dopa decarboxylase than the much smaller amounts of dopa. The prompt fall in homovanillic acid excretion suggests that α-methyldopamine and α-methylnoradrenaline are being formed equally promptly.

If the view of Day & Rand about the action of the drug is correct, it would be expected that the excretion of normetadrenaline would rise shortly after the drug was given, as noradrenaline was being displaced from its storage sites. Only after noradrenaline had been displaced would α-methylnoradrenaline start to be released.

Our results agree with this. The excretion of normetadrenaline rose in the first few hrs after the drug, but it was not until after this initial rise had subsided that α-methylnormetadrenaline began to appear in the urine.

During the period when the excretion of normetadrenaline was high, the patients' blood pressures were raised. This is consistent with there being a slightly increased circulating blood level of noradrenaline. It is interesting that during the same period the normal subject's blood pressure did not rise, though his excretion of normetadrenaline did. A possible explanation is that the blood pressure homeostatic mechanisms are more effective in normal persons than in hypertensive patients.

Gjessing (1964a,b; 1965) studied patients with periodic catatonia and found pronounced overactivity of the sympathetic nervous system during the psychotic stupor phase. He found that after treatment with α-methyldopa the excretion of α-methylnormetadrenaline followed the course of the disease in the same manner as did the excretion of normetadrenaline. Gjessing's results strongly suggest that after treatment with α-methyldopa, α-methylnoradrenaline is released when sympathetic nerves are stimulated.

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