Action of Guanethidine on the 5-Hydroxytryptamine Content of the Brain

SIR,—As guanethidine decreases the level of noradrenaline in the brain of the rat (Pfeifer, Vizi and Sàtory, 1962; Kroneberg and Schümann, 1962), it seemed interesting to us to investigate the effect of guanethidine on the 5-hydroxytryptamine (5-HT) content of the brain. In addition we compared α-methyldopa (an inhibitor of 5-hydroxytryptophan decarboxylase) and reserpine with guanethidine.

White rats of both sexes and of different ages were used. Brain 5-HT content was estimated by the procedure described by Bertaccini (1960). Guanethidine, DL-α-methyldopa and reserpine were administered once daily for 7 or 12 days. Animals were killed 16–24 hr. after the last drug administration.

TABLE I

EFFECT OF GUANETHIDINE, DL-α-METHYLDOPA AND RESERPINE ON 5-HT CONTENT, AS THE FREE BASE, OF THE BRAIN IN WHITE RATS OF BOTH SEXES AND OF DIFFERENT WEIGHTS FOLLOWING REPEATED SUBCUTANEOUS ADMINISTRATIONS

Compound	Sex	Weight of rats g.	No. of rats	Dose mg./kg. × days	Brain 5-HT content		P
					mean μg./g. tissue	per cent decrease	
NaCl 0·9 per cent							
Controls	male	200–300	24	—	0·39 ± 0·06	—	—
Guanethidine	male	200–300	16	10×7	0·24 ± 0·07	−38·5	<0·01
α-Methyldopa	male	200–300	8	200×7	0·19 ± 0·09	−51·3	<0·01
Reserpine	male	200–300	8	1×7	0·048 ± 0·034	−88	<0·01
NaCl 0·9 per cent							
Controls	female	280–320	6	—	0·57	—	—
Guanethidine	female	280–320	6	10×12	0·28	−50·9	—
NaCl 0·9 per cent ..							
Controls	male	140–160	20	—	0·250	—	—
Guanethidine	male	140–160	8	10×7	0·245	−0·2	—

It can be seen from Table I that rats weighing more than 200 g. have a significantly higher 5-HT level in the brain than rats weighing only 140–160 g.

Guanethidine, following repeated administrations at dosage which reduces blood pressure in the rat with renal hypertension (Bein, 1960), decreases cerebral 5-HT content in rats of both sexes weighing more than 200 g. Guanethidine seems to be ineffective in rats weighing 140–160 g. Except for a slight palpebral ptosis no overt behavioural changes were present in the animals treated by guanethidine. α-Methyldopa and reserpine seem to be more effective in reducing the brain 5-HT level than guanethidine.

We cannot explain why guanethidine decreases the brain 5-HT content of rats weighing 200–300 g. but not of those weighing 140–160 g. It has been shown (Green and Furano, 1962) that neoplastic mast cells contain two pools of amines: the endogenous amines are held in a pool separate from exogenous amines. Endogenous amines turn over at rates different from the exogenous amines (Day and Green, 1962). It may be, in our experiments there is a similar situation and possibly only a part of the amines present can be influenced by guanethidine.

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REFERENCES

Bein, H. J. (1960). *Adrenergic Mechanisms*, 162–170. London: J. and A. Churchill Ltd.
Bertaccini, G. (1960). *J. Physiol.*, **153**, 239–249.
Day, M. and Green, J. P. (1962). *Biochem. Pharmacol.*, **11**, 1043–1048.
Green, J. P. and Furano, A. V. (1962). *Ibid.*, **11**, 1049–1053.
Kroneberg, G. and Schümann, H. J. (1962). *Arch. exp. Path. u. Pharmak.*, **243**, 16–25.
Pfeifer, A. K., Vizi, E. Sz. and Sàtory, E. (1962). *Biochem. Pharmacol.*, **2**, 397–398.

Urinary Phenols in Patients Treated with α-Methyldopa

SIR,—There is still some doubt about the mode of action of the hypotensive drug α-methyldopa.

It was originally introduced because Sourkes (1954) had shown that in high concentration it blocked the conversion of dopa to dopamine by inhibiting dopa decarboxylase and thus inhibiting catecholamine formation.

Other workers (Gillespie and others, 1962; Pletscher, 1963) have suggested that α-methyldopa's hypotensive action is due to its reserpine-like property of depleting the body stores of catecholamines.

Recently, Day and Rand (1963) suggested that it inhibited the conversion of dopa to dopamine by competing for dopa decarboxylase, being itself converted to α-methyldopamine. This, in turn, was converted to α-methylnoradrenaline which displaced noradrenaline from the storage sites at sympathetic nerve endings. Here it was held as a "false neurotransmitter" and was released in response to sympathetic nerve stimulation. Having a pressor activity much less than that of noradrenaline, the blood pressure fell.

It seemed likely that a study of the urinary excretion of the metadrenalines and the phenolic acids 4-hydroxy-3-methoxymandelic acid (HMMA) and homovanillic acid (HVA) after the administration of α-methyldopa might throw some light on this problem.

Hypertensive patients were fasted overnight. A control sample of urine was collected over a period of 2 hr. The patient was then given an oral dose of DL-α-methyldopa (usually 250 mg.) and no food was allowed for a further 4 hr.

Urine samples were collected over successive 2 hr. periods for 8 to 12 hr. The patient remained in bed throughout the test.

Phenolic acids were extracted and separated by two dimensional chromatography as described by Robinson and others (1959). The metanephrines were isolated by the method of Robinson and Smith (1962), separated chromatographically, and estimated spectrophotometrically after their oxidation to vanillin.

Two hours after the administration of the α-methyldopa the HVA excretion had fallen to about 50 per cent of that in the control period. Two hr. later, it could scarcely be detected on the chromatogram and 8 hr. after giving the α-methyldopa, HVA was undetectable on the chromatogram.

During the same period there was a slight rise in the excretion of HMMA and a significant rise in the excretion of the metadrenalines.

About 10 to 12 hr. after the dose of α-methyldopa, a compound appeared in the urine which was tentatively identified as α-methylnormetanephrine.

Our results are in accord with Day and Rand's hypothesis. The early reduction in HVA excretion reflects the dopa decarboxylase inhibition at this stage. The increased excretion of both metadrenaline and normetadrenaline