Letters to the Editor

Inhibition of ^{3}H-metaraminol uptake by antidepressive and related agents

SIR,—In a previous paper we have reported a dual amine uptake mechanism of the adrenergic nerve (Carlsson & Waldeck, 1965). As an indicator of amine uptake ^{3}H-metaraminol was used. It was found that reserpine, a drug acting on the granular storage mechanism, did not inhibit the initial uptake of ^{3}H-metaraminol but greatly increased its rate of disappearance. In contrast, desipramine, a drug acting on the amine transport mechanism of the axon membrane of the adrenergic nerve, almost completely inhibited the neuronal uptake of ^{3}H-metaraminol. We have now extended our investigation to a number of other antidepressive and related agents.

Usually, 10 mg/kg of the test substances was given intravenously to mice 5 min before the intravenous administration of 0·02 mg/kg ^{3}H-metaraminol and the animals were killed 30 min later. ^{3}H-metaraminol in the heart was estimated as described earlier (Carlsson & Waldeck, 1965). The results are presented in Table 1.

TABLE 1. INHIBITION OF ^{3}H-METARAMINOL UPTAKE BY ANTIDEPRESSIVE AND RELATED AGENTS IN THE HEARTS OF MICE

Group	Compound tested	Inhibition of ^{3}H-metaraminol uptake as % of control
I	Protriptyline[1]	9
	Desipramine	9
	Ro 4–6011[2]	16
	Nortriptyline	22
	Imipramine	25
	Dibenzepin (Noveril)[3]	30
	Amitriptyline	32
II	Guanethidine	35
	Chlorpromazine	42
	Amphetamine (5 mg/kg)	46
	Cocaine	46
	Bretylium	53
	BW392C60[4] (5 mg/kg)	54
	Ph 879/4–07155[5]	57
III	Reserpine (i.p. 6 hr before)	78
	Prenylamine	62
	Prenylamine (30 min before)	111
	Trimiprimine	90
	Haloperidol	119
	Promethazine	98
	Prochlorperazine	105
	Phenoxybenzamine	110
	Azapetine	116
	Atropine	125
	Ouabain (2 mg/kg)	114
	Controls (Mean of 21 experiments = 46·3 ng/g tissue)	100 ± 14 s.d.

In general the values are the mean of two determinations.

[1] 5-(3-Methylaminopropyl)-5*H*-dibenzo[*a*,*d*]cycloheptene.
[2] 5-(3-Methylamino propylidene)-5*H*-dibenzo[*a*, *d*]cycloheptene HCl.
[3] 10-(2-Dimethylaminoethyl)-10,11-dihydro-5-methyl-11-oxo-5-dibenzo[*b*,*e*][1,4]-diazepine HCl.
[4] *N*-*o*-Chlorobenzyl-*N*′*N*″-dimethylguanidine.
[5] 7-Amino-5,6,8,9-tetrahydro-7*H*-benzocycloheptene.

The drugs have been divided into 3 groups according to potency. Compounds listed in group I belong to the thymoleptic series of drugs. All proved to be potent inhibitors of the cell membrane transport mechanism. This is in agreement with the finding that they potentiate the effects of noradrenaline (Sigg, 1959; Haefely, Hürlimann & Thoenen, 1964; Stone, Porter, Stavorski, Ludden & Totaro, 1964): when the neuronal uptake is inhibited more noradrenaline will reach the receptors.

Group II includes drugs with moderate activity. Some of them have been shown earlier to inhibit the uptake of noradrenaline in the heart of the rat (Axelrod, Hertting & Potter, 1962). Most of them have other, probably more important, effects.

The compounds belonging to group III showed little or no effect in this test. Some of the drugs, like reserpine, prenylamine (Segontin), phenoxybenzamine and azapetine, have previously been shown to inhibit the uptake of catecholamines by the granules of the adrenal medulla (Carlsson, Hillarp & Waldeck, 1963). Using the perfused rat heart, Iversen (1965) found reserpine and phenoxybenzamine to inhibit the uptake of ^{14}C-noradrenaline. His technique, however, does not distinguish between inhibition of uptake at the cell membrane level and inhibition of the granular storage mechanism. After the latter type of inhibition, noradrenaline can still be transported into the intracellular space but will, in contrast to metaraminol, be destroyed by the action of monoamine oxidase, and thus little or no accumulation can occur (cf. Hillarp & Malmfors, 1964; Lindmar & Muscholl, 1964).

It is interesting to note that methylation of imipramine on the second side-chain carbon—resulting in trimiprimine (Surmontil)—leads to much reduction of activity. Trimiprimine is described as a thymoleptic with strong sedative properties.

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References

Axelrod, J., Hertting, G. & Potter, L. (1962). *Nature, Lond.*, **194**, 297.
Carlsson, A., Hillarp, N.-Å. & Waldeck, B. (1963). *Acta physiol. scand.*, **59**, suppl. 215.
Carlsson, A. & Waldeck, B. (1965). *Acta Pharm. Tox. Kbh.* In the press.
Haefely, W., Hürlimann, A. & Thoenen, H. (1964). *Helv. Phys. Pharm. Acta*, **22**, 15–33.
Hillarp, N.-Å. & Malmfors, T. (1964). *Life Sci.*, **3**, 703–708.
Iversen, L. L. (1965). *J. Pharm. Pharmacol.*, **17**, 62–64.
Lindmar, R. & Muscholl, E. (1964). *Arch. exp. Path. Pharmak.*, **247**, 469–492.
Sigg, E. B. (1959). *Canad. Psychiat. Ass. J.*, **4**, 75–85.
Stone, C. A., Porter, C. C., Stavorski, J. M., Ludden, C. T. & Totaro, J. A. (1964). *J. Pharmacol.*, **144**, 196–204.