Reversal by amphetamine of the protective effect of bretylium on reserpine-induced depletion of noradrenaline

SIR,—Bretylium has been shown to prevent the depletion of noradrenaline caused by many agents such as guanethidine (Kuntzman, Costa, Gessa & Brodie, 1962), reserpine (Callingham & Cass, 1962; Inesi, Pekkarinen, Hess, Shanfeld & Haugaard, 1962; Ryd, 1962; Arnold, McAuliff, Sobell & Archer, 1963) and metaraminol (unpublished observation). Release of noradrenaline on splenic nerve stimulation is also inhibited by bretylium (Boura & Green, 1959; Hertting, Axelrod & Patrick, 1962). On the other hand, the anti-hypertensive effect of bretylium is antagonized by amphetamine (Wilson & Long, 1960). Further, Matsumoto & Horita (1962) and Day (1962) have shown that the adrenergic neurone blocking effect of bretylium is reversed by amphetamine. It is interesting in this connection that Brodie, Chang & Costa (1965) showed that the uptake of bretylium in the rat heart was inhibited by amphetamine although it was not made certain whether the inhibition of bretylium binding is associated directly with the antagonism of adrenergic neurone blockade.

It seemed of interest, therefore, to see whether the effect of (+)-amphetamine extends to the protective action of bretylium on the drug-induced depletion of noradrenaline. Reserpine was used as a noradrenaline depleting agent since amphetamine itself does not interfere with the effect of reserpine (Table 1) while noradrenaline depletion by other agents, such as guanethidine (Matsumoto & Horita, 1963; Chang, Costa & Brodie, 1965) and metaraminol (unpublished observation), is interfered with. Noradrenaline in the rat heart was assayed by a modified trihydroxyindole method (Chang, 1964).

TABLE 1. EFFECT OF AMPHETAMINE ON THE PREVENTION BY BRETYLIUM OR GUANETHIDINE OF RESERPINE-INDUCED NORADRENALINE DEPLETION IN THE RAT HEART

Rats were treated (i.p.) with the drugs 30 min before administration of reserpine (i.v.) with or without 1·0 mg/kg of amphetamine (i.p.) given 30 min before the pretreatments. Rats were killed 5 hr after administration of reserpine.

Pretreatment	Dose of reserpine (mg/kg)	Noradrenaline as % of normal	
		Without amphetamine	With amphetamine
None	0·32	3 ± 0·8 (9)	5 ± 1·3 (3)
Bretylium, 10 mg/kg	,,	46 ± 1·2 (5)*	8 ± 2·2 (3)**
Guanethidine, 10 mg/kg	,,	10 ± 0·9 (4)*	6 ± 2·0 (4)
None	1·0	1 ± 0·4 (6)	1 ± 0·2 (3)
Bretylium, 10 mg/kg	,,	12 ± 1·2 (6)*	2 ± 0·2 (5)**
Guanethidine, 10 mg/kg	,,	9 ± 1·3 (5)*	2 ± 0·3 (4)**

* $P < 0.05$ vs reserpine alone. ** $P < 0.05$ vs without amphetamine.

Fig. 1 shows that when the rat was pretreated with bretylium (10 mg/kg) the depletion of noradrenaline by reserpine was markedly inhibited, thus causing the dose-response curve of reserpine to be shifted almost in parallel to the right. It should be noted, however, that, in the animal pretreated with bretylium, it becomes impossible to have a complete depletion by reserpine even at higher doses (Fig. 1). This fact indicates a non-competitive nature of the antagonism between reserpine and bretylium. The broken line in Fig. 1 shows the effect of amphetamine (1 mg/kg) upon the action of bretylium. The dose-response curve affected by bretylium was shifted back to the left by amphetamine pretreatment and reserpine resumed its activity to induce a maximal depletion of noradrenaline. The data in Table 1 show that guanethidine also interfered with the action of

reserpine to some extent and the effect, like that of bretylium, was reversed by amphetamine.

Since bretylium appears not to act competitively with reserpine for the prevention of noradrenaline depletion, and, in contrast to amphetamine (Chang & others, 1965), prevents the noradrenaline depletion induced by guanethidine without inhibiting the binding of the latter drug (Brodie & others, 1965), it is likely that bretylium acts by a similar mechanism against divergent depleting agents. For such a common mechanism it may be assumed that bretylium interferes with the release from the nerve endings of the noradrenaline which is effected either by reserpine, guanethidine, metaraminol or possibly by nerve

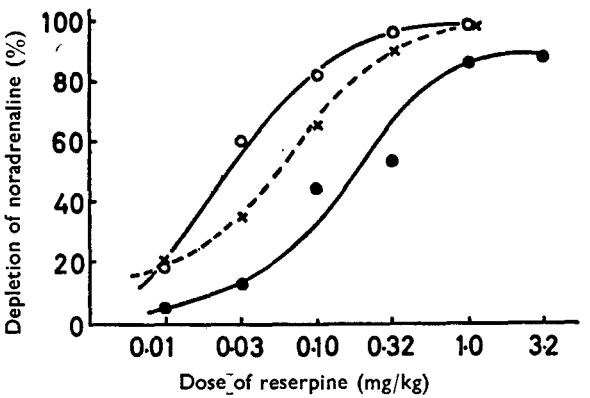

FIG. 1. Effects of amphetamine and bretylium on the noradrenaline depletion induced by various doses of reserpine in the rat heart. Rats were pretreated with bretylium (10 mg/kg; i.p.) and 30 min later with reserpine (i.v.). Amphetamine (1 mg/kg; i.p.) was given 30 min before administration of bretylium. Animals were killed 5 hr after the reserpine injection. Each point represents mean % depletion of heart noradrenaline from three to eight experiments. ○———○, reserpine alone; ●———●, bretylium plus reserpine; ×———×, amphetamine plus bretylium plus reserpine.

impulses. Amphetamine may interfere with the binding of bretylium to the target site and thus antagonizes the actions of bretylium; the site of binding, however, may be different from the site at which amphetamine and guanethidine compete (Chang & others, 1965; Brodie & others, 1965).

Acknowledgement. I am grateful to the National Council on Science Development, Republic of China, for a grant for animals and materials.

C. C. CHANG

Pharmacological Institute,
College of Medicine,
National Taiwan University,
Taipei, Taiwan.
October 23, 1965

References

Arnold, A., McAuliff, J. P., Sobell, S. D., & Archer, S. (1963). *Biochem. Pharmacol.*, **12**, 1231–1232.
Boura, A. L. A. & Green, A. F. (1959). *Brit. J. Pharmacol.*, **14**, 536–548.
Brodie, B. B., Chang, C. C. & Costa, E. (1965). *Ibid.*, **25**, 171–178.
Callingham, B. A. & Cass, R. (1962). *J. Pharm. Pharmacol.*, **14**, 385–389.

Chang, C. C. (1964). *Int. J. Neuropharmacol.*, **3**, 643–649.
Chang, C. C., Costa, E. & Brodie, B. B. (1965). *J. Pharmacol.*, **147**, 303–312.
Day, M. D. (1962). *Brit. J. Pharmacol.*, **18**, 421–439.
Hertting, G., Axelrod, J. & Patrick, R. W. (1962). *Ibid.*, **18**, 161–166.
Inesi, G., Pekkarinen, A., Hess, M. E., Shanfeld, J. & Haugaard, N. (1962). *Biochem. Pharmacol.*, **11**, 1089–1093.
Kuntzman, R., Costa, E., Gessa, G. L. & Brodie, B. B. (1962). *Life Sci.*, **3**, 65–74.
Matsumoto, C. & Horita, A. (1962). *Nature, Lond.*, **195**, 1212–1213.
Matsumoto, C. & Horita, A. (1963). *Biochem. Pharmacol.*, **12**, 295–297.
Ryd, G. (1962). *Acta physiol. scand.*, **56**, 90–93.
Wilson, R. & Long, C. (1960). *Lancet*, **2**, 262.

Effects of certain tranquillisers on the level of homovanillic acid in the corpus striatum

SIR,—Earlier investigations have shown that chlorpromazine or haloperidol increase the levels of dihydroxyphenylacetic acid and homovanillic acid but not of 5-hydroxyindoleacetic acid in the corpus striatum of the rabbit (Andén, Roos & Werdinius, 1964). This increase occurs without any concomitant change in tissue monoamine levels. The first biochemical evidence of an influence on the monoamine metabolism *in vivo* by chlorpromazine and haloperidol was the observation that the accumulation of methoxytyramine and normetanephrine in brain after treatment with a monoamine oxidase inhibitor was enhanced by chlorpromazine or haloperidol (Carlsson & Lindqvist 1963). There is some evidence for the view that the elimination of the dopamine acid metabolites is retarded by the two drugs but other data support the suggestion that the synthesis of the acid metabolites is increased. Against the former and in favour of the latter hypothesis are the facts that the dihydroxyphenylacetic acid and homovanillic acid levels increase simultaneously and that 5-hydroxyindoleacetic acid is unchanged after chlorpromazine or haloperidol.

It is known that these drugs may block both peripheral and central effects of catecholamines. The blockade of the catecholamine receptors of the effector cells may have the effect of increasing the release of transmitter from the neurones with a compensatory stimulation of the catecholamine synthesis. In this instance it might be possible to assume that a stronger inhibition of the receptor may result in a greater increase of the levels of the phenolic acids in the brain. Homovanillic acid is formed from dihydroxyphenylacetic acid after the attack by the enzyme catechol-*O*-methyl transferase. This reaction is so far not known to be influenced by chlorpromazine or haloperidol.

The effect of 15 tranquillising substances has been investigated by giving them intravenously to rabbits. The homovanillic acid was measured 3 hr after the injection by the method developed in this laboratory (Andén & others, 1963) (Table 1). The animals were kept in a warm environment. Hypothermia can thus be excluded as a causative factor in the changes of the acid metabolites after these drugs.

It is interesting to note that major tranquillisers with a well-known antipsychotic effect, such as perphenazine, triflumethazine and clopenthixol, also strongly increase the homovanillic acid level. On the other hand, phenothiazines used as minor tranquillisers, for instance, prothipendyl or promazine hydrochloride, have only a slight effect, or none at all, on the level of the acid. The substances R6109 and R5147 are derivatives of the butyrophenone made by Janssen Ltd. in Belgium. Like haloperidol they seem to have a rather strong effect on homovanillic acid levels. Further work on the possible connection between the antipsychotic action and the homovanillic acid-increasing effects of tranquillising drugs is in progress.