The interaction of dexamphetamine with inhibitors of noradrenaline biosynthesis in rat brain *in vivo*

SIR,—It is known that sodium diethyl dithiocarbamate (DDC) is an inhibitor of dopamine-β-hydroxylase (Goldstein, Anagoste & others, 1964) and that DDC decreases tissue noradrenaline content, presumably as a consequence of this action (Collins, 1965; Carlsson, Lindqvist & others, 1966). Similiarly 3-iodo-L-tyrosine has been shown to be a potent inhibitor of the enzyme tyrosine hydroxylase (Goldstein & Weiss, 1965; Ikeda, Levitt & Udenfriend, 1965) and to decrease tissue levels of both noradrenaline and dopamine (Goldstein, Anagoste & Nakajima, 1965). In addition, Anden, Fuxe & Hökfelt (1966) have demonstrated the importance of impulse flow for the depletion of brain amines by synthesis-inhibitors. Thus an increase in impulse flow in any neuron will cause a more rapid depletion of amines from that neuron if biosynthesis is inhibited. Corrodi, Fuxe & Hökfelt (1966) have recently made use of this principle to demonstrate the inhibitory effect of barbiturates on dopamine turnover in the brain. I have applied a similar technique to study the effect of the central stimulant drug, dexamphetamine, on turnover of brain catecholamines.

Although dexamphetamine at high dose levels is known to cause a decrease in brain noradrenaline and dopamine, Smith (1965) has pointed out that the excitant action of the drug can be produced with doses which cause no change in brain noradrenaline levels and which raise brain dopamine levels. It was thought that these low doses of dexamphetamine might be producing some change in impulse flow in noradrenaline and dopamine-containing neurons which was not reflected in changes in total brain catecholamines. Accordingly, the interaction of a low dose of dexamphetamine with the noradrenaline synthesis inhibitors DDC and 3-iodo-L-tyrosine has been examined. The results are in Table 1.

Adult, male, white rats of 180–220 g weight were used. All injections were made subcutaneously in volumes of 1 ml. Estimations of noradrenaline and dopamine were by the method of Brownlee & Spriggs (1965).

TABLE 1. EFFECTS OF DEXAMPHETAMINE ON THE CHANGES IN RAT BRAIN CATECHOLAMINE CONTENT PRODUCED BY INHIBITORS OF NORADRENALINE BIOSYNTHESIS. Percentages, and standard errors are compared with uninjected controls. (Each value represents the mean of eight determinations.) The absolute values for control brains were noradrenaline 0·38 ± 0·02 μg/g, and dopamine 0·62 ± 0·05 μg/g.

Treatment	Duration (hr)	% Noradrenaline	% Dopamine
3-Iodo-L-tyrosine 200 mg/kg s.c. ..	1	60 ± 2·5	50·5 ± 3·5
	3	62·5 ± 3·5	55·0 ± 2·0
3-Iodo-L-tyrosine 200 mg/kg + dexamphetamine 2 mg/kg s.c. ..	1	82 ± 3·0	79 ± 4·7
	3	64 ± 3·2	75 ± 4·2
DDC 500 mg/kg s.c.	1	60 ± 2·6	99 ± 5·7
	3	50 ± 1·0	146 ± 7·0
DDC 500 mg/kg + dexamphetamine 2 mg/kg s.c. ..	1	87 ± 2·7	147 ± 7·5
	3	60·5 ± 2·0	144 ± 8·2
Dexamphetamine 2 mg/kg s.c.	1	97 ± 2·5	126 ± 6·1
	3	89 ± 4·5	118 ± 5·2

3-Iodo-L-tyrosine caused a fall both in the dopamine and in the noradrenaline content of rat brain; DDC caused a fall in noradrenaline and a rise in brain dopamine levels. A small dose of dexamphetamine (2 mg), which when administered alone caused no significant change in brain noradrenaline levels, reduced the rate of depletion of brain noradrenaline by both synthesis inhibitors when injected with them. The depletion of brain dopamine by 3-iodo-L-tyrosine

was also inhibited but in view of the increased brain dopamine levels produced in rat brain by this dose of dexamphetamine, this result is of doubtful significance. The rise in brain dopamine after DDC was not affected consistently by the dose of dexamphetamine.

There are several possible explanations for these results. Dexamphetamine may have interfered with the passage of the synthesis-inhibitors to the site of catecholamine biosynthesis or may have modified their action in some other way. The comparatively low dose of dexamphetamine which I used reduces the likelihood of competition with the synthesis-inhibitors for any site of action or uptake. Alternatively, the results may arise from a reduction in transmitter output from central noradrenaline neurons. If this is so, then it is unlikely that the sympathomimetic properties of dexamphetamine can be ascribed either to an increase in adrenergic transmitter release or to a decrease in transmitter re-uptake (Glowinski & Axelrod, 1965), since both these actions would have the effect of accelerating the depletion of noradrenaline after the inhibition of synthesis. It seems more likely that dexamphetamine has a direct effect on central noradrenaline receptors.

The apparent reduction in noradrenaline turnover may originate in either an inhibitory feedback from the central receptors or in a direct effect of dexamphetamine on the neuronal membrane—which inhibits the passage of noradrenaline across it.

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References

Anden, N. E., Fuxe, F. & Hökfelt, T. (1966). *J. Pharm. Pharmac.*, **18**, 630–633.
Brownlee, G. & Spriggs, T. L. B. (1965). *Ibid.*, **17**, 429–433.
Carlsson, A., Lindqvist, M., Fuxe, K. & Hokfelt, T. (1966). *Ibid.*, **18**, 60–62.
Collins, G. G. S. (1965) *Ibid.*, **17**, 526–527.
Corrodi, J., Fuxe, K. & Hökfelt, T. (1966). *Ibid.*, **18**, 556–558.
Glowinski, J. & Axelrod, J. (1965). *J. Pharmac. exp. Ther.*, **149**, 43–49.
Goldstein, M., Anagoste, B., Lauber, E. & McKereghan, M. R. (1964). *Life Sci.*, **3**, 763–767.
Goldstein, M., Anagoste, B. & Nakajima, K. (1965). *Biochem. Pharmac.*, **14**, 1914–1916.
Goldstein, M. & Weiss, Z. (1965). *Life Sci.*, **4**, 261–263.
Ikeda, M., Levitt, M. & Udenfriend, S. (1965). *Biochim biophys. Res. Commun.*, **18**, 482.
Smith, C. B. (1965). *J. Pharmac. exp. Ther.*, **147**, 96–102.