The effects of (+)-amphetamine and (±)-phenmetrazine on the noradrenaline and dopamine levels in the hypothalamus and corpus striatum of the rat

Sir,—(+)-Amphetamine decreases and (±)-phenmetrazine increases whole rat brain noradrenaline levels (Baird & Lewis, 1964). This effect of (+)-amphetamine supports the current view that it acts by releasing noradrenaline from the brain (Stein, 1964; Carlsson, Lindqvist & others, 1965; Weissman, Koe & Tenen, 1966) while that of (±)-phenmetrazine suggests a different mechanism of action although its effects on behaviour resemble those of (+)-amphetamine (Van der Schoot, Ariëns & others, 1962; Weissman & others, 1966). However, these conclusions must be tentative as precise mechanisms of action cannot be deduced from observations on whole brain. Nevertheless, further investigation appeared warranted. Noradrenaline is unevenly distributed in the brain and as a first step, an area of the brain rich in the amine, the hypothalamus (Vogt, 1954), was used since drug-induced changes in its noradrenaline content are more likely to reflect the true action of the compounds on brain noradrenaline levels. In addition, the hypothalamus is concerned with mood and behaviour (Ingram, 1960). Therefore, the effects of (+)-amphetamine and (±)-phenmetrazine on the level of noradrenaline in the rat hypothalamus were investigated.

Drug (in 0·9% w/v NaCl solution) and control (0·9% w/v NaCl solution) solutions were injected intraperitoneally (0·2 ml/100 g body weight) into groups of 4 male rats (80–110 g). Three hr later, the animals were killed and the hypothalamic areas dissected and pooled. The pooled tissues were homogenized in ice-cold 0·4M perchloric acid, extracted and the noradrenaline adsorbed onto acid-washed alumina at pH 8·5. The amine was eluted with 0·2N acetic acid and assayed fluorimetrically by the trihydroxyindole method.

The results are shown in Table 1. As in whole brain, (+)-amphetamine reduces the hypothalamic noradrenaline level but (±)-phenmetrazine, although it increases the noradrenaline level in whole brain, does not affect it in the hypothalamus. These observations further support the view that (+)-amphetamine acts indirectly by releasing noradrenaline from the brain and suggest that

TABLE 1. THE EFFECTS OF (+)-AMPHETAMINE AND (±)-PHENMETRAZINE ON THE LEVELS OF NORADRENALINE AND DOPAMINE IN THE HYPOTHALAMUS AND CORPUS STRIATUM OF THE RAT BRAIN

Treatment	Dose mg/kg	No. of groups	Noradrenaline (μg/g fresh hypothalamus)	Dopamine (μg/g fresh corpus striatum)
Control	0	5	4·54 ± 0·34	—
(+)-Amphetamine sulphate	10	5	3·34 ± 0·22**	—
Control	0	8	6·13 ± 0·66	—
(±)-Phenmetrazine hydrochloride	40	8	7·48 ± 1·11	—
Control	0	7	5·07 ± 0·30	—
(±)-Phenmetrazine hydrochloride	80	7	4·16 ± 0·30	—
Control	0	5	—	10·68 ± 0·59
(+)-Amphetamine sulphate	10	5	—	12·38 ± 0·53
Control	0	5	—	9·51 ± 0·59
(+)-Amphetamine sulphate	20	5	—	10·28 ± 1·11
Control	0	5	—	8·94 ± 0·39
(±)-Phenmetrazine hydrochloride	80	5	—	10·61 ± 0·57*

All values are the means ± standard errors of the means. The animals (4 in each group) were killed 3 hr after the intraperitoneal injection of the drug or control solution. Significance of difference from control: * $0{\cdot}05 > P > 0{\cdot}02$; ** $0{\cdot}02 > P > 0{\cdot}01$.

noradrenaline may not be involved in the mode of action of (±)-phenmetrazine.

Since dopamine may be involved in psychomotor stimulation (Rossum, 1964), the possibility that the central actions of (±)-phenmetrazine are mediated through this amine was explored by measuring the effect of this drug on the dopamine level in the rat corpus striatum, an area rich in dopamine (Bertler & Rosengren, 1959). The experiments were made as described above for the hypothalamus except that dopamine was assayed by the method of Udenfriend (1962). The effect of (+)-amphetamine on the dopamine level in the rat corpus striatum was also examined.

The results are shown in Table 1. (±)-Phenmetrazine increases the dopamine level in the rat corpus striatum which may account for the increased motor activity it produces since increasing amounts of brain dopamine are paralleled by increasing motor activity (Everett & Wiegand, 1962). On the other hand, (+)-amphetamine does not affect the amount of dopamine in the rat corpus striatum suggesting that its central actions are not mediated through this amine.

The reported results suggest that (+)-amphetamine and (±)-phenmetrazine, in spite of their chemical and pharmacological similarity, do not have a common mode of action in the brain. A link apparently exists between (+)-amphetamine and noradrenaline, which is decreased, and between (±)-phenmetrazine and dopamine, which is increased. Therefore, it is possible that these amines are involved in the respective central mechanisms of action of the drugs.

Acknowledgements. I am grateful to Miss Frances P. Moore for skilful technical assistance, to Smith, Kline and French Laboratories for a gift of (+)-amphetamine and to Boehringer Ingelheim Ltd. for a gift of (±)-phenmetrazine.

Department of Pharmacology,
University of Glasgow,
Glasgow, W.2,
Scotland.

J. R. C. BAIRD

December 12, 1967

References

Baird, J. R. C. & Lewis, J. J. (1964). *Biochem. Pharmac.*, **13**, 1475–1482.
Bertler, A. & Rosengren, E. (1959). *Experientia*, **15**, 10–11.
Carlsson, A., Lindqvist, M, Dahlström, A., Fuxe, K. & Masuoka, D. (1965). *J. Pharm. Pharmac.*, **17**, 521–524.
Everett, G. M. & Wiegand, R. G. (1962). *Proceedings of the First International Pharmacological Meeting*, Vol. 8, editors Paton, W. D. M. & Lindgren, P., pp. 85–92, Oxford, London: Pergamon Press.
Ingram, W. R. (1960). *Handbook of Physiology*, Section 1: Neurophysiology, Vol. 2, editors Field, J., Magoun, H. W. & Hall, V. E., pp. 951–978, Washington, D.C.: American Physiological Society.
Rossum, J. M. van. (1964). *Proceedings of the Second International Pharmacological Meeting*, Vol. 2, editors Trabucchi, E., Paoletti, R. & Canal, N., pp. 115–126, Oxford London, Edinburgh: Pergamon Press.
Stein, L. (1964). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **23**, 836–850.
Udenfriend, S. (1962). *Fluorescence Assay in Biology and Medicine*, p. 137, London: Academic Press.
Van der Schoot, J. B., Ariëns, E. J., Rossum, J. M. van & Hurkmans, J. A. Th. M. (1962). *Arzneimittel-Forsch.*, **12**, 902–907.
Vogt, M. (1954). *J. Physiol., Lond.*, **123**, 451–481.
Weissman, A., Koe, B. K. & Tenen, S. S. (1966). *J. Pharmac. exp. Ther.*, **151**, 339–352.