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Activity of centrally acting drugs on amphetamine metabolism

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Amitriptyline, nortriptyline and dibenzepine prolong the increase in temperature produced by amphetamine in rats and also increase the level of brain amphetamine above that effected by amphetamine alone. After chlorpromazine and propericiazine, brain amphetamine levels are also higher but the rise of body temperature elicited by amphetamine is inhibited. Phenelzine prolongs and α-methyl-*p*-tyrosine inhibits the rise in body temperature without modifying the accumulation of brain amphetamine. In reserpinized rats amphetamine causes a temperature increase several degrees greater than in control animals although its level in the brain is lower.

IMIPRAMINE and other tricyclic antidepressant agents prolong pharmacological and behavioural effects of amphetamine (Carlton, 1961; Stein, 1964, 1967; Lapin & Schelkunov, 1965) and in particular potentiate the increase in body temperature it induces (Morpurgo & Theobald, 1965; Jori & Garattini, 1965). Imipramine and desipramine given before amphetamine may potentiate its pharmacological activity allowing an increase in its brain and other tissue levels (Valzelli, Consolo & Morpurgo, 1967) probably by inhibiting its metabolism to *p*-hydroxyamphetamine (Consolo, Dolfini & others, 1967).

It is of interest to establish if drugs acting on the central nervous system interfere with the metabolism of amphetamine. We have related brain amphetamine concentrations to its temperature raising effect which is central in origin (Belenky & Vitolina, 1962).

Experimental

Male Sprague-Dawley rats weighing 165 ± 5 g were used. They were kept five to a Makrolon cage (38 × 22 × 15 cm) at 22° and 60% relative humidity, and fed *ad libitum* up to the beginning of the experiment.

(±)-Amphetamine sulphate was given intraperitoneally at either 7·5 or 15 mg base/kg. Its concentrations in brain and liver were determined according to Axelrod (1954a,b). Body temperature was recorded by an electrical thermometer inserted in the rectal cavity.

The drugs tested were the hydrochlorides of amitriptyline (Merck Sharp & Dohme), nortriptyline (Pharmacia), dibenzepine (Wander), chlorpromazine (Farmitalia) and phenelzine (Warner-Lambert), propericiazine free base (Farmitalia), α-methyl-*p*-tyrosine (Merck Sharp & Dohme) and reserpine free base (Serpasil vials, CIBA). All were administered intraperitoneally at doses in terms of the bases. These drugs when added to the brain and liver *in vitro* did not interfere with the assay of amphetamine. No amphetamine-like products were detected in the brains of rats injected with the test drugs.

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Results

Table 1 summarizes the influence of amitriptyline, nortriptyline and dibenzepine on the increase in body temperature induced by amphetamine and on the levels of brain amphetamine. There is a significant prolongation of the temperature increase and a rise in brain amphetamine concentration above that effected by the same dose of amphetamine alone.

TABLE 1. EFFECT ON THREE TRICYCLIC ANTIDEPRESSANT AGENTS ON THE LEVEL OF BRAIN AMPHETAMINE AND ON BODY TEMPERATURE AFTER ADMINISTRATION OF (+)-AMPHETAMINE (7·5 MG/KG I.P.) IN RATS PRETREATED WITH NORTRIPTYLINE OR DIBENZEPINE

Drug (D)	Time (hr) after amphet-amine (A)	Brain amphetamine (μg/g ± s.e.)		Body temperature (°C ± s.e.)		
		A	D + A	D	A	D + A
Amitriptyline (10 mg/kg, i.p.)	1	4·6 ± 0·5	6·5 ± 0·1*	36·9 ± 0·3	38·7 ± 0·3	39·1 ± 0·4
	2	2·7 ± 0·4	3·8 ± 0·4	37·0 ± 0·2	38·4 ± 0·4	39·7 ± 0·2*
	3	1·0 ± 0·1	1·8 ± 0·2*	37·2 ± 0·4	37·8 ± 0·2	39·2 ± 0·3*
	4	0·8 ± 0·01	1·8 ± 0·2	37·1 ± 0·3	37·8 ± 0·5	39·2 ± 0·4*
Nortriptyline (10 mg/kg, i.p.)	1	3·9 ± 0·1	6·6 ± 0·1*	37·0 ± 0·3	39·5 ± 0·2	39·3 ± 0·3
	2	2·0 ± 0·2	4·3 ± 0·4*	37·1 ± 0·2	38·7 ± 0·4	39·2 ± 0·4
	3	1·7 ± 0·2	3·0 ± 0·1*	37·4 ± 0·3	38·2 ± 0·3	39·2 ± 0·2
Dibenzepine (5 mg/kg, i.p.)	1	5·0 ± 0·1	8·2 ± 0·3*	37·0 ± 0·3	39·1 ± 0·3	39·1 ± 0·4
	2	1·9 ± 0·1	4·6 ± 0·1*	37·2 ± 0·3	38·6 ± 0·4	39·2 ± 0·3
	3	1·8 ± 0·1	3·8 ± 0·1*	37·0 ± 0·4	38·5 ± 0·3	39·3 ± 0·3*
	4	0·7 ± 0·1	1·3 ± 0·1	37·1 ± 0·2	38·3 ± 0·2	38·6 ± 0·4

* P 0·01 in respect of animals receiving (+)-amphetamine only. Control body temperature was 37·2 ± 0·4°.
Each figure is the average of at least eight determinations. A, animals treated with amphetamine. D + A, animals treated with the drug 1 hr before amphetamine.

Table 2 shows that after chlorpromazine and propericiazine there was also a brain amphetamine concentration above that found after amphetamine alone. But both drugs decreased the rise in temperature caused by amphetamine.

TABLE 2. EFFECT OF CHLORPROMAZINE AND OF PROPERICIAZINE ON THE LEVEL OF BRAIN AMPHETAMINE AND ON BODY TEMPERATURE FOLLOWING THE ADMINISTRATION OF (+)-AMPHETAMINE

Drug (D)	Time (hr) after amphet-amine (A)	Brain amphetamine (μg/g ± s.e.)		Body temperature (°C ± s.e.)		
		A	D + A	D	A	D + A
Chlorpromazine (15 mg/kg, i.p.)	1*	13·8 ± 1·6	19·3 ± 1·8†	32·2 ± 0·3	40·1 ± 0·3	35·2 ± 0·4†
	2	4·6 ± 0·9	11·0 ± 0·6†	32·5 ± 0·2	39·4 ± 0·2	36·2 ± 0·2†
	4	1·3 ± 0·6	6·8 ± 0·8†	33·2 ± 0·4	37·8 ± 0·3	36·7 ± 0·6†
Chlorpromazine (15 mg/kg, i.p.)	1**	7·1 ± 0·6	11·6 ± 0·9	36·1 ± 0·2	39·8 ± 0·2	35·4 ± 0·3†
	2	2·8 ± 0·3	6·0 ± 0·4	36·3 ± 0·4	39·6 ± 0·3	35·2 ± 0·3†
	4	0·3 ± 0·2	3·7 ± 0·2	35·9 ± 0·3	38·2 ± 0·3	36·2 ± 0·3†
Propericiazine (5 mg/kg, i.p.)	0·5**	7·2 ± 0·4	10·3 ± 0·8†	35·9 ± 0·2	38·7 ± 0·4	36·2 ± 0·3†
	1	4·1 ± 0·4	7·3 ± 0·7†	35·5 ± 0·5	39·0 ± 0·4	36·2 ± 0·4†
	2	2·6 ± 0·6	4·0 ± 0·2†	35·3 ± 0·5	38·7 ± 0·4	36·5 ± 0·4†
	3	1·9 ± 0·3	3·1 ± 0·4†	35·9 ± 0·7	38·6 ± 0·2	37·0 ± 0·3†
	4	1·3 ± 0·3	3·2 ± 0·4†	36·6 ± 0·6	37·7 ± 0·2	38·1 ± 0·2
Propericiazine (2·5 mg/kg, i.p.)	0·5**	8·9 ± 0·3	6·8 ± 0·7	37·0 ± 0·2	39·0 ± 0·2	36·7 ± 0·2†
	1	5·2 ± 0·5	5·3 ± 0·5	35·9 ± 0·3	39·5 ± 0·2	37·4 ± 0·2†
	2	2·5 ± 0·3	2·5 ± 0·3	35·1 ± 0·3	39·5 ± 0·3	37·5 ± 0·2†

A = animals treated with amphetamine (*) 15 mg/kg i.p. or (**) 7·5 mg/kg i.p.
D = animals treated with the drug. D + A = animals treated with the drug 1 hr before amphetamine.
† P < 0·01 in respect of animals receiving amphetamine only. Control body temperature was 37·2 ± 0·4°.
Each figure is the average of at least eight determinations.

Table 3 shows that phenelzine did not affect the brain amphetamine level but prolonged the hyperthermic response of amphetamine. Reserpinized animals were markedly hypothermic but the temperature raising effect of amphetamine was apparent although, as with the level of brain amphetamine, it was lower than when amphetamine was given alone. α-Methyl-*p*-tyrosine, a blocker of catecholamine synthesis (Spector, Sjoerdsma & Udenfriend, 1965), did not change the level of brain amphetamine but decreased the temperature-raising effect of amphetamine.

TABLE 3. EFFECT OF DRUGS AFFECTING BRAIN AMINES ON THE LEVEL OF BRAIN AMPHETAMINE AND ON BODY TEMPERATURE FOLLOWING THE ADMINISTRATION OF (+)-AMPHETAMINE

Drug (D)	Time (hr) after amphetamine (A)	Brain amphetamine (μg/g ± s.e.)		Body temperature (°C ± s.e.)		
		A	D + A	D	A	D + A
Phenelzine (20 mg/kg, i.p. 1 hr before amphetamine)	1*	14·2 ± 0·8	15·8 ± 0·3	37·2 ± 0·3	41·3 ± 0·3	41·5 ± 0·2
	2	10·4 ± 0·6	10·4 ± 0·7	37·4 ± 0·2	40·4 ± 0·4	40·8 ± 0·3
	4	2·8 ± 0·5	2·3 ± 0·6	37·8 ± 0·4	38·7 ± 0·4	40·3 ± 0·4†
Reserpine (2·5 mg/kg, i.p. 16 hr before amphetamine)	1*	11·1 ± 0·5	8·8 ± 0·8†	33·3 ± 0·5	40·2 ± 0·6	36·5 ± 0·3†
	2	4·8 ± 0·8	2·4 ± 0·6†	32·7 ± 0·8	39·2 ± 0·4	37·8 ± 0·4†
	4	1·9 ± 0·5	2·0 ± 0·3	33·4 ± 0·8	38·9 ± 0·3	38·2 ± 0·2
α-Methyltyrosine (300 mg/kg, i.p. 2 hr before amphetamine)	1*	14·2 ± 0·7	13·8 ± 0·5	37·4 ± 0·6	41·0 ± 0·6	40·1 ± 0·3†
	2	9·4 ± 0·5	9·1 ± 0·6	37·7 ± 0·4	40·1 ± 0·5	39·2 ± 0·7
	4	3·2 ± 0·6	4·9 ± 0·8	37·6 ± 0·3	38·9 ± 0·3	38·4 ± 0·3
α-Methyltyrosine (150 mg/kg 4 hr and 150 mg/kg 2 hr before amphetamine)	1**	3·7 ± 0·2	3·7 ± 0·5	37·1 ± 0·4	39·2 ± 0·2	37·7 ± 0·3†
	2	1·9 ± 0·6	1·3 ± 0·6	36·5 ± 0·5	38·4 ± 0·3	38·2 ± 0·3
	4	0·3 ± 0·1	1·3 ± 0·2	36·0 ± 0·5	37·9 ± 0·3	37·1 ± 0·3†

A = animals treated with amphetamine (*) 15 mg/kg i.p. or (**) 3·75 mg/kg i.p.
D = animals treated with the drug. D + A = animals treated with the drug before amphetamine.
Control body temperature was 37·2 ± 0·4°.
† $P < 0{\cdot}01$ in respect to animals treated only with amphetamine.
Each figure is the average of at least six determinations.

Discussion

Although amphetamine is used as a tool to detect potential psychotropic drugs or to explore adrenergic functions in the central nervous sytem, little information has usually been given about its level in the brain in various experimental situations.

Previous studies have indicated the importance of knowing such information. For instance the increase in concentration of amphetamine in the brain of aggregated mice was greater than that in isolated animals (Consolo, Garattini & others, 1965). This suggests that the enhanced toxicity and the increased depletion of brain catecholamines (Moore, 1963) in aggregated mice, may be partially explained by the differences in the concentration of amphetamine. The potentiation of amphetamine activity by desipramine (Morpurgo & Theobald, 1965) might in part be explained as a blockade of the hydroxylation of amphetamine (Consolo & others, 1967) leading to an increase in brain amphetamine (Valzelli & others, 1967; Sulser, Owens & Dingell, 1966).

The prolongation by amitriptyline, nortriptyline and dibenzepine of the temperature increase induced by amphetamine, agrees with the work of Morpurgo & Theobald (1965). This prolongation can be explained on the basis that brain amphetamine is increased by about 50% when these antidepressant drugs are given before amphetamine.

Valzelli & others (1967) pointed out that the temperature increase is less than might be expected from the brain amphetamine level. This suggests that amitriptyline, nortriptyline and dibenzepine may have a neuroleptic (phenothiazine-like) effect.

The capacity to increase the level of amphetamine in the brain is shared by phenothiazines such as chlorpromazine and propericiazine. But the temperature increase elicited by amphetamine is blocked (Morpurgo & Theobald, 1965; Moore, 1964; Galambos, Pfeiffer & others, 1967; Herman, 1967).

Monoamine oxidase inhibitors potentiate the toxicity of amphetamine (Brittain, Jack & Spencer, 1964; Herman, 1967). In our experiments phenelzine prolonged the hyperthermia induced by amphetamine but the brain levels of amphetamine were unaffected.

Reserpine decreases the level of brain amphetamine perhaps because of its hypothermic effect. Despite the lower levels of brain amphetamine and temperature, the temperature increase was several degrees greater in reserpinized animals given amphetamine than in controls receiving the amphetamine alone. Amphetamine activity is increased in reserpinized animals (Beauvallet, Fugazza & others, 1966; Quinton & Halliwell, 1963; Morpurgo & Theobald, 1966; Rech, 1964; Smith, 1963, 1964) although the duration of action may be shortened (Morpurgo & Theobald, 1966; Herman, 1967; Quinton & Halliwell, 1963) and the amine is less toxic (Moore, 1964; Rudzik & Mennear, 1966).

α-Methyl-*p*-tyrosine reduces the increase in temperature caused by amphetamine although the levels of the drug in brain were comparable to control animals. This finding corroborates data of Dingell, Owens & others (1967) and the hypothesis that antagonism observed between α-methyl-*p*-tyrosine and amphetamine (Hanson, 1966, 1967; Weissman, Koe & Tenen, 1966; Mennear & Rudzik, 1966; Menon, Dandiya & Bapna, 1967) argues for the central action of amphetamine being mediated by catecholamines (Hanson, 1967).

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