Biochemical Pharmacology, Vol. 17, pp. 633–634. Pergamon Press. 1968. Printed in Great Britain

SHORT COMMUNICATIONS

Metabolism of amphetamine in tumour bearing rats

(*Received* 28 *November* 1967; *accepted* 7 *December* 1967)

PREVIOUS studies indicate that the metabolism of pentobarbital is reduced in tumour bearing rats[5]. It was therefore interesting to establish if a similar effect could be observed also for other drugs such as amphetamine which are hydroxylated in rats[1–4] through the microsomal enzymes of the liver.

Male Sprague–Dawley rats of the average weight of 120 g, received an s.c. transplant of Walker 256 carcinosarcoma. Sixteen days after transplantation when the tumour weighed about 20 g and the animals were still in general satisfactory condition, a dose of *d*-amphetamine sulphate (10 mg/kg) was given i.p. At several times after administration, liver, brain and tumour amphetamine were determined. In other rats, all the urine was collected for 24 hr after the administration of the same dose of *d*-amphetamine sulphate. Control rats without tumours were similarly treated. Determinations of amphetamine and *p*-OH-amphetamine were carried out in biological specimens according to Axelrod.[2, 3] Even though a certain amount of amphetamine was present in the tumour, results reported in Table 1 indicate that liver and brain amphetamine are considerably higher in tumour bearing than in control rats.

TABLE 1. TISSUE AMPHETAMINE LEVELS IN NORMAL AND WALKER-TUMOUR BEARING RATS

N. rats	Body wt. without tumour (g ± S.E.)	Group	Tumour wt. (g ± S.E.)	Time after amphetamine (min)	μg Amphetamine/g tissue		
					Liver	Brain	Tumour
8	240 ± 11	Normal	—	30	11·6 ± 0·9	11·9 ± 1·0	—
8			—	60	6·5 ± 0·6	4·9 ± 0·6	—
8			—	120	3·8 ± 0·3	2·9 ± 0·2	—
8			—	180	3·4 ± 0·2	2·2 ± 0·4	—
8			—	240	1·6 ± 0·6	0·8 ± 0·3	—
8	173 ± 8	Walker 16 days old	19·9 ± 4·4	30	14·1 ± 0·8	12·7 ± 0·8	5·9 ± 1·0
8			22·1 ± 2·1	60	13·0 ± 0·9*	6·7 ± 0·5‡	4·7 ± 0·8
8			21·6 ± 6·5	120	11·2 ± 0·4*	4·2 ± 0·4	1·1 ± 0·1
8			17·5 ± 3·6	180	4·3 ± 0·8	3·0 ± 0·6	n.m.
8			19·4 ± 2·0	240	4·0 ± 0·5†	1·5 ± 0·3	n.m.

* $P < 0·01$.

† $P = 0·05$.

‡ $P < 0·05$ in respect to normal, n.m. = not measurable.

Table 2 shows that the higher levels of tissue amphetamine in tumour bearing rats could be explained by the reduced hydroxylation of amphetamine.

These results suggest that liver microsomal enzymes may be impaired in their activity during tumor growth. Further studies are in progress.

This work was financially supported by contract DHEW/PHS/NIH PH-43-67-83.

TABLE 2. DETERMINATION OF AMPHETAMINE AND *p*.OH-AMPHETAMINE IN URINE. URINES WERE POOLED IN 8 SAMPLES

N. rats	Body wt. without tumour (g ± S.E.)	Group	Tumour wt. (g ± S.E.)	Urine ml/rat	Urine pH	Amphetamine μg/ml	*p*.OH-amphetamine μg/ml
12	240 ± 10	Normal	—	5·1	6·9	80·3 ± 1·1	74·7 ± 4·5
12	152 ± 10	Walker 16 days old	20·7 ± 2·7	5·3	7·0	109·0 ± 1·0*	25·5 ± 2·8*

* $P < 0.01$ in respect to normal.

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Biochemical Pharmacology, Vol. 17, pp. 634–636. Pergamon Press. 1968. Printed in Great Britain

Potentiation and blockade of the central action of amphetamine by chlorpromazine*

(*Received* 4 *August* 1967; *accepted* 24 *October* 1967)

RECENT evidence suggests that the central stimulatory action of amphetamine is mediated through the release of newly synthesized norepinephrine.[1–3] Moreover, amphetamine might enhance the action of the released norepinephrine by blocking its reuptake.[4] Desipramine (DMI) and other tricyclic antidepressants, which also block the amine-concentrating mechanism of central norepinephrine fibers,[5, 6] have been shown to enhance and prolong the central stimulatory action of amphetamine in the rat.[7–9] The enhanced action of amphetamine after the administration of DMI however, appears to be the consequence of an inhibition of the metabolism of amphetamine by DMI.[10, 11] Stein[12] has reported that chlorpromazine can also prolong the action of amphetamine. The prolongation of the action of amphetamine by chlorpromazine however, is observed only after the administration of low doses of the tranquilizer.

The present studies were undertaken to determine whether this effect of chlorpromazine might also be the consequence of a change in the distribution or metabolism of amphetamine. Male Sprague–Dawley rats (180–200 g) were used. The drugs were administered intraperitoneally, *d*-amphetamine as the sulfate and chlorpromazine as the hydrochloride salt. *d*-Amphetamine-^{3}H-sulfate (generally labeled, 4·23 c/m-mole) was obtained from the New England Nuclear Corp. The drug was assayed by a modification of the method of Axelrod[13] as previously described.[10] Psychomotor stimulation was measured in Williamson activity cages. Various doses of chlorpromazine were given i.p. 45 min before a standard dose of 3 mg/kg of *d*-amphetamine. The psychomotor activity was measured over a period of 10 hr.

* Supported by National Institutes of Health Research Grant MH11468 from the U.S. Public Health Service.