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

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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.

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Low doses of chlorpromazine (1·25–2·5 mg/kg) markedly enhance the central action of *d*-amphetamine (Fig. 1). For example, rats pretreated with 1·25 mg/kg of chlorpromazine showed marked psychomotor stimulation as long as 10 hr after amphetamine, whereas animals receiving only amphetamine displayed psychomotor stimulation for about 3 hr. Higher doses of chlorpromazine

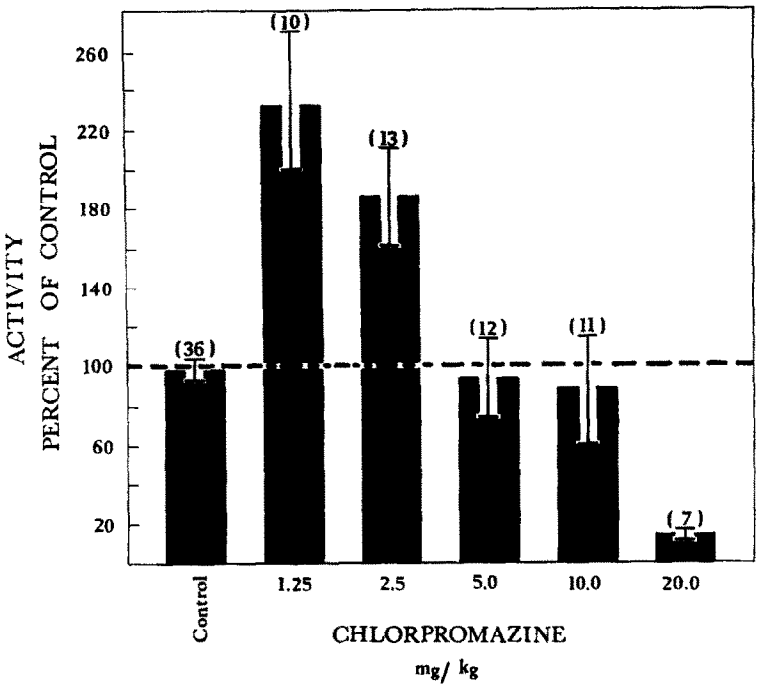

FIG. 1. The effect of various doses of chlorpromazine on the psychomotor stimulation elicited by *d*-amphetamine. The activity was measured over a period of 10 hr and is expressed as a percentage of the activity of the rats receiving amphetamine alone. The number of animals is in parentheses. Vertical bars indicate the S.E.M.

antagonize or block the action of amphetamine (Fig. 1). The measurement of ^{3}H-*d*-amphetamine in brain revealed that both low and high doses of chlorpromazine cause a marked and prolonged elevation of the levels of *d*-amphetamine (Table 1). For example, after pretreatment with chlorpromazine

TABLE 1. THE EFFECT OF VARIOUS DOSES OF CHLORPROMAZINE ON THE LEVEL OF ^{3}H-*d*-AMPHETAMINE IN BRAIN

Chlorpromazine* (mg/kg)	^{3}H-*d*-amphetamine in brain (μg/g)	
	1 hr	6 hr
Experiment 1		
none	2·32 ± 0·20	0·10 ± 0·02
1·25	4·04 ± 0·62	0·49 ± 0·13
2·50	3·86 ± 0·68	0·92 ± 0·23
10·0	5·35 ± 0·42	1·17 ± 0·25
Experiment 2		
none	2·20 ± 0·29	0·06 ± 0·02
10·0	5·40 ± 0·39	1·56 ± 0·14
20·0	5·26 ± 0·73	2·12 ± 0·70

* Chlorpromazine was administered i.p. to rats 45 min before ^{3}H-*d*-amphetamine (3 mg/kg, i.p.). The results are expressed as the mean values obtained with 6 rats ± S.D.

(1·25 to 2·5 mg/kg), the brain levels of amphetamine 6 hr after its administration were 5- to 9-fold greater than those of the control animals. At these low doses the adrenergic blocking action of chlorpromazine does not appear sufficient to prevent the action of the norepinephrine which is released in the presence of increased amounts of amphetamine. In contrast, higher doses of chlorpromazine antagonize the action of emphetamine even in the presence of strikingly elevated levels of amphetamine in brain (Table 1). Since the action of amphetamine appears to depend on the release of newly synthesized norepinephrine, the data obtained with high doses of chlorpromazine furnish additional evidence for the central adrenergic blocking properties of this phenothiazine derivative. This interpretation is consistent with recently obtained data by Bradley *et al.*,[14] whose studies demonstrated that chlorpromazine specifically blocked the excitatory effects elicited by norepinephrine on single neurons of the brain stem reticular formation. Moreover, the results of the present study explain the desipramine-like potentiation of the action of amphetamine by low doses of chlorpromazine.

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The duration of the inhibition of glutamine synthetase by methionine sulfoximine*

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METHIONINE sulfoximine (MSO) is a powerful convulsant whose mode of action remains obscure. Sellinger and Weiler[1] showed that this compound competitively inhibits rat cerebral glutamine synthetase *in vitro*. Lamar and Sellinger[2] demonstrated that glutamine synthetase isolated from brains of rats treated with MSO, when compated to untreated controls, was affected in a manner described for noncompetitive inhibition.[3] These and other studies involving the incubation *in vitro* of glutamine synthetase, ATP, magnesium, 2, 3 dimercaptopropanol, and 1-^{14}C-MSO in the presence and absence of glutamate led to the hypothesis that MSO inhibited this enzyme either by causing a permanent

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