by investigating the effect of drug pretreatment on the ability of *p*-chloroamphetamine to lower rat brain 5-HT levels. Intraperitoneally administered Org 6582 was approximately twice as potent as fluoxetine, five times more potent than chlorimipramine and 14 times more potent that desipramine in blocking the ability of *p*-chloroamphetamine to lower brain 5-HT content. Org 6582, whilst having no effect on amine steady-state levels, decreased rat brain 5-HT turnover. Rat brain 5-hydroxyindole acetic acid (5-HIAA) levels were also decreased by Org 6582. The reduction in both 5-HT turnover and 5-HIAA levels is in all probability due to re-uptake blockade.

Peripheral *in vivo* blockade of NA re-uptake was determined by measuring the effect of drug pretreatment on the ability of (−)-metaraminol to lower rat heart NA levels. The i.p. ID_{50} values for desipramine and chlorimipramine were 5.5 mg/kg and 29.6 mg/kg respectively. Org 6582 (60 mg/kg i.p.) did not antagonize the (−)-metaraminol-induced fall in rat heart NA content. Central catecholaminergic re-uptake was studied by investigating the effect of i.p. drug pretreatment on the ability of intraventricularly administered 6-hydroxydopamine (100 μg) to lower rat brain NA and dopamine (DA) levels. The 6-hydroxydopamine-induced fall in rat brain DA content was unaltered by the prior injection of either Org 6582 (60 mg/kg), chlorimipramine (60 mg/kg) or desipramine (30 mg/kg). Pretreatment with either chlorimipramine (60 mg/kg) or desipramine (30 mg/kg), but not with Org 6582 (60 mg/kg), blocked the reduction in brain NA content elicited by 6-hydroxydopamine. Org 6582 had no effect either on steady-state levels or on the turnover of NA and DA in the rat brain.

The results of this study reveal Org 6582 to be a potent selective inhibitor of 5-HT re-uptake.

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Effect of LSD on rat brain 5-hydroxytryptamine metabolism at elevated environmental temperature

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Rat brain tryptophan and 5-hydroxyindoleacetic acid (5-HIAA) concentrations (Tagliamonte, Tagliamonte, Perez-Cruet, Stern & Gessa, 1971) and the firing of 5-hydroxytryptamine (5-HT) containing neurones (Weiss & Aghajanian, 1971) are increased at elevated temperature. The latter two changes appear related, as both are blocked by D-lysergic acid diethylamide (LSD) (Weiss & Aghajanian, 1971). Their relationship to the tryptophan increase is unclear as although this can increase brain 5-HT turnover (Tagliamonte *et al.*, 1971; Knott & Curzon, 1972) additional 5-HT formed is not necessarily released to the synapse. Therefore, we have studied the effects of a 40° C environment on tryptophan disposition and on brain 5-HT metabolism and their modification by LSD.

Male Sprague-Dawley rats (180-200 g) were caged in eight groups of three in a chamber at 25° ± 2° C. Four groups were transferred to a chamber at 40° ± 3° C for 60 min and then killed. LSD tartrate (500 μg/kg i.p.) was given to two of the test groups (40° C) immediately before transfer, and to two control (25° C) groups. Plasma tyrosine, total and free tryptophan and brain tyrosine, tryptophan, 5-HT and 5-HIAA were determined (Curzon, Joseph & Knott, 1972; Knott & Curzon, 1972).

Exposure to 40° C increased plasma total and free tryptophan but not percentage free tryptophan. Brain tryptophan increased markedly, 5-HIAA moderately and 5-HT was not significantly altered (Table 1). Plasma and brain tyrosine were significantly increased (75 and 95% respectively). LSD had no significant effect on either brain or plasma tryptophan, but significantly decreased 5-HIAA (Table 1). The fall was greater at 40° C so that the drug treated rats at both temperatures had similar values.

In another experiment, the rats were given L-tryptophan (50 mg/kg i.p.) 15 min after transfer to the 40° C chamber and then killed 45 min later.

Table 1 Effects of LSD and raised environmental temperature on plasma free and total tryptophan and brain tryptophan, 5-HT and 5-HIAA

	Plasma		*Brain*		
	Total tryptophan µg/ml	*Free tryptophan µg/ml*	*Tryptophan µg/g*	*5-HT µg/g*	*5-HIAA µg/g*
Control (25°C) (n = 6)	13.6 ± 4.0	2.01 ± 0.31	3.02 ± 0.52	0.76 ± 0.04	0.56 ± 0.04
Control + LSD (500 µg/kg i.p.) (n = 6)	14.8 ± 2.5	2.43 ± 0.39	3.23 ± 0.36	0.76 ± 0.06	0.48 ± 0.05 *
40°C (n = 6)	28.9 ± 3.6 **	4.39 ± 0.60 **	9.04 ± 2.43 **	0.88 ± 0.09	0.72 ± 0.07 **
40°C + LSD (500 µg/kg i.p.) (n = 6)	25.3 ± 0.4 **	3.60 ± 0.73 **	7.85 ± 1.16 **	0.83 ± 0.12	0.49 ± 0.04 ***

Rats placed in 40° C environment for 60 min, LSD administered at the start of this period, n = no. of rats
Results given as mean ± s.d.
* Significantly different from control (25°C) $P < 0.02$
** Significantly different from control (25°C) $P < 0.01$
*** Significantly different from 40°C $P < 0.01$

Tryptophan increased both brain 5-HT and 5-HIAA. In 40° C LSD pretreated rats, tryptophan caused a significantly smaller 5-HIAA increase, while that of 5-HT tended to be greater.

The results indicate that the increased 5-HIAA in rats exposed to 40° C is not obviously related to increased plasma and brain tryptophan. Also, LSD appeared to decrease catabolism of 5-HT formed from *exogenous* tryptophan at 40° C. If this, like the decreased catabolism of *endogenous* 5-HT after LSD, is caused by decreased release of 5-HT at the synapse, then it implies that exogenous tryptophan can cause increased 5-HT release. Other findings are in agreement (Barasi & Roberts, 1974; Marsden & Curzon, 1975).

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