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The Relation between Cerebral Serotonin Levels and Conditioned Behaviour in the Rat following the Administration of LSD-25 and UML

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Abstract. Successive daily injections of LSD-25 and UML (1-methyl-*d*-lysergic acid butanolamide) caused progressive depression of brain 5-HT levels in the rat. On the fourth day, the decrease was significant with respect to the highly significant fall observed after a single administration, whereas it had been shown earlier that conditioned behaviour is no longer affected by LSD-25 after 3 days and that simultaneous administration of a single dose of LSD-25 and UML is equally ineffective in this respect. Its depression of 5-HT levels, however, has now been shown to be equal to that of LSD-25 alone at doses that influence conditioned behaviour. The findings indicate that changes in such behaviour are not dependent on brain 5-HT levels and that no link exists between such levels and the psychotomimetic effect of LSD-25 in man.

Key words: LSD-25 – UML – Acute – Chronic – Behaviour – 5-HT – Brain – Rat.

A recent personal paper in this journal (Torre *et al.*, 1974) showed that 0.5 mg/kg lysergic acid diethylamide (LSD-25) caused a significant decrease in brain serotonin content in the rat. 1-Methyl-*d*-lysergic acid butanolamide (UML) has the same effect. This dose also leads to significant deterioration of conditioned avoidance behaviour in the case of LSD-25, whereas UML has no such effect (Torre and Fagiani, 1968).

The two drugs have similar formulae and antiserotonin activity, and it was therefore suggested that the effect of LSD-25 on behaviour was not related to brain serotonin levels. This hypothesis might also explain why UML, unlike LSD-25, has no psychotomimetic effect in man. Torre (1972) has shown that 0.5 mg/kg LSD-25 and 3 mg/kg UML administered simultaneously have no effect on the conditioned avoidance reflex, i.e. UML overrides LSD-25, possibly a result of competition. LSD-25 itself loses its effect on the reflex as from the third day when given alone at a dose of 0.5 mg/kg/day (Torre and Fagiani, 1972). Freedman *et al.* (1958) observed a similar situation in non-conditioned learning, using doses of 0.13–0.26 mg/kg. Tolerance without dependence is rapid when LSD-25 is taken voluntarily (McGlothlin and Arnold, 1971). It is for this reason that "trips" are–and, indeed, must be–taken at distinct intervals to make sure they are effective.

The present paper examines whether 1. differences in behaviour noted by Torre (1972) and Torre and Fagiani (1972) are related to changes in brain 5-HT levels, and 2. whether the effect of repeated administration of LSD-25 and UML on these levels differs from the depression observed after a single dose.

Simultaneous administration of these drugs for their effect on cerebral 5-HT does not appear to have been previously studied.

Diaz and Huttunen (1971) noted a significant increase (13%) in levels in the rat 18 hrs after 0.2 mg/kg/day LSD-25 for 1 month.

Methods

Male Wistar albino rats weighing about 250 g were used.

In the first series of experiments, LSD-25 and UML (0.5 mg/kg intraperitoneally in both cases) were always

Table 1

	Brain 5-HT levels (μg/g)					
	controls	LSD acute* (0.5 mg/kg)	LSD chronic (0.5 mg/kg/day)	UML acute* (0.5 mg/kg)	UML chronic (0.5 mg/kg/day)	LSD (0.5 mg/kg) + UML (3 mg/kg)
Mean S.D. ($n = 8$)	412 ± 60	350 ± 36	310 ± 37	354 ± 50	288 ± 35	367 ± 17
Student's t respect to controls		2.348 $P < 0.05$	4.080 $P < 0.01$	2.014 $P < 0.1$	5.060 $P < 0.01$	Student's t respect to LSD acute: 1.219
Student's t acute/chronic		2.216 $P < 0.05$		3.070 $P < 0.01$		

* From: M. Torre, F. Bogetto and E. Torre: Effect of LSD-25 and 1-methyl-*d*-lysergic acid butanolamide on rat brain and platelet serotonin levels. Psychopharmacologia (Berl.) **36**, 117–122 (1974).

given at the same hour on four consecutive days. Brains were removed 10 min after the last injection, i.e. on the fourth day.

In the second series, brains were removed 10 min after a single intraperitoneal dose of 0.5 mg/kg LSD-25 and 3 mg/kg UML.

The controls received equivalent volumes of saline.

After decapitation, the brain was removed as quickly as possible and placed at 0° C for a few minutes before 5-HT extraction. The incision was made at the lower part of the myelencephalon to enable 5-HT values to be determined on the whole organ.

5-HT was extracted according to the method of Shore and Olin (1958) and readings were taken with an Aminco-Bowman spectrophotofluorimeter.

Results

By the fourth day of daily administration of LSD-25 (when no effect on conditioned behaviour is observed) a highly significant decrease in serotonin levels occurred ($P < 0.01$, using Student's t test) by comparison with the controls ($P < 0.05$ by comparison with the levels observed after administration of the single dose). The same results were obtained with UML.

An analysis of variance was performed with three parameters (A = treatment; B = drugs; C = administration modality–acute and chronic) to achieve a clearer statistical picture. The single-administration data reported by Torre *et al.* (1974) were used for parameter C.

The following results were obtained:

$A - F = 46.65$, $P < 0.01$: the effect of treatment as a whole (i.e. both drugs and both methods) was highly significant.

$A \times B - F = 0.12$: the difference between the effects of the two drugs was not significant.

$B \times C - F = 0.26$: the difference between the effects of the two drugs with respect to the modalities of treatment was not significant.

$A \times C - F = 4.29$, $P < 0.05$: the difference between acute and chronic treatment was significant.

The results of administration of LSD-25 and UML simultaneously in a single dose shows that there was no significant difference with respect to LSD-25 alone.

Discussion

Two points emerge from our findings, firstly that brain serotonin levels change irrespective of their possible relation to changes in conditioned behaviour. Depression by LSD-25 and UML is independent of dose in the range 0.1–3.5 mg/kg (as shown in both this and our previous study), while levels are significantly decreased on the fourth day by comparison with the first when 0.5 mg/kg are administered daily.

This difference between the effect of variable as opposed to repeated doses cannot as yet be explained, but is interesting from a biochemical and pharmacological standpoint. It may be suggested that lower doses block all 5-HT-producing factors active at the moment of administration, but not those that are not operating. This block remains irrespective of the permanence of the drug, so that an increase in dose has no additional effect. In the case of chronic administration, on the other hand, further depression of levels results from the progressive inhibition of factors as they become active.

Relation between serotonin levels and conditioned behaviour. It would seem that the changes in-

duced by LSD-25 are not dependent on such levels, since the effect on behaviour noted after a single dose is no longer apparent on the fourth day of chronic administration, while a continuing and significant fall in 5-HT values is observed over the same period.

Apart from this obvious discrepancy, there is also the fact that UML shows the same depression of 5-HT, but has no effect on behaviour at all. Lastly, a simultaneous injection of LSD-25 and UML, while devoid of effect on behaviour, since UML blocks the specific action of LSD-25, nevertheless causes a fall in 5-HT values that is not significantly different from that observed with LSD-25 alone.

The suggestion that LSD-25 modifies 5-HT turnover, whereas UML does not, even though both drugs have the same influence on levels, cannot be put forward as an explanation for their diverse effect on behaviour in the light of our data.

The present findings, therefore, are in line with the view we expressed earlier, namely that there is no link between psychotomimetic effect and 5-HT levels in man, such levels being equally unassociated with changes in conditioned behaviour in the rat.

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