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The influence of 1-methyl-D-lysergic acid butanolamide on gastrointestinal serotonin in the Sprague–Dawley rat*

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D-LYSERGIC acid diethylamide (LSD-25) antagonizes the effect of serotonin on the rat uterus.[1] Sankar *et al.*[2, 3] have reported increased levels of serotonin in several brain areas and visceral organs in the rabbit (they omitted the gastrointestinal tract), after LSD-25. Similarly, Freedman,[4] and Freedman and Giarman[5] have reported small but definite elevations of cerebral serotonin after LSD-25 pretreatment. Of the many derivatives of LSD-25, 1-methyl-*d*-lysergic acid butanolamide (UML 491: Sansert, Sandoz Pharmaceuticals, Inc.), has been shown to be a more potent serotonin antagonist than LSD-25 in several tissues.[6, 7] Consequently, the effect of this drug on the bowel serotonin concentration in rats has been investigated.

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Male Sprague–Dawley rats, weighing between 200 and 300 g, from the Charles River Laboratories (breeding shed 1) were maintained on normal Purina rat chow with a tryptophan content of 0·22 per cent. The rats were housed in colony cages and exposed to a regular 24-hr light/dark cycle (light, 5 a.m.–7 p.m.). The rats were randomly divided into two groups and injected i.p. with UML 491, 1·0 mg/kg, or with normal saline, 2·0 ml/kg. The animals were killed by decapitation between 8 and 9 a.m. on the day of assay and the following tissues excised: stomach fundus, body, and pyloric antrum; upper and lower duodenum; upper and mid-jejunum; terminal ileum; appendix; cecum; ascending, transverse, and descending colon; and rectum. After removal, the tissues were opened longitudinally, cleaned, and blotted dry. The mucosa was separated from the muscle and its serotonin content assayed spectrophotofluorometrically by the method of Bogdanski *et al.*[8] Where enough tissue was available, duplicate samples were run. In the determination of the time response to 1-methyl-D-lysergic acid butanolamide (UML 491), upper jejunal mucosa was used. Upper jejunum was selected because of the ease of removal, the availability of duplicate samples, and the narrow range in variability from one segment to the next. Significance between the saline-injected and the UML 491-injected rats was determined by the Student's *t* test.

Jejunal mucosal serotonin as a function of time after UML 491 is indicated in Fig. 1. It can be seen that control saline-injected rats gave a value of 7·14 ± 0·13 μg/g, which is similar to values obtained previously.[9–11] After UML 491, the jejunal mucosal serotonin concentration increased. The peak response of 8·92 ± 0·29 μg/g developed at 60 min ($P < 0·001$), with values of 8·20 ± 0·33 μg/g at 30 min ($P < 0·005$), and 8·14 ± 0·25 μg/g at 120 min ($P < 0·001$). Return to control levels occurred by 4 hr.

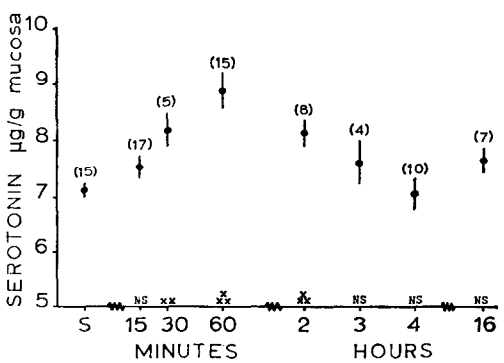

FIG. 1. Jejunal mucosal serotonin expressed as mean ±1 S.E. at various times after UML 491 (1 mg/kg) or saline. The number of rats is indicated in parentheses, and the P values between the saline-injected group (S), and each of the UML-491-treated groups are indicated: NS = not-significant, $\overset{x}{xx} = P < 0·001$, $xx = P < 0·005$.

This peak response developing at 60 min differs somewhat from data already published for cerebral serotonin and LSD-25. Freedman[4] asserted that LSD-25 (0·130 mg/kg) in reserpine—pretreated rats (1 mg/kg), precipitated a two-fold elevation of cerebral serotonin at 20, 60, and 120 min, and at 24 hr post injection. Subsequently, Freedman and Giarman[5] indicated that LSD-25-treated rats, sacrificed 10, 20, or 120 min after injection, demonstrated a statistically higher cerebral serotonin concentration, but UML 491 was without effect.

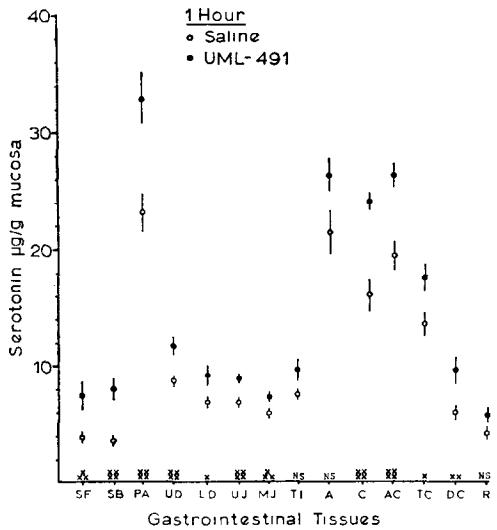

FIG. 2. Mean values ±1 S.E. for serotonin in the stomach fundus (SF); stomach body (SB); pyloric antrum (PA); upper and lower duodenum (UD, LD); upper and mid-jejunum (UJ, MJ); terminal ileum (TI); appendix (A); cecum (C); ascending, transverse and descending colon (AC, TC, DC); and rectum (R) 1 hr after UML 491 or saline injections. Each point is the mean of 7–14 animals. P values are indicated: NS = not significant, $\overset{xx}{xx}$ = P < 0·001, $\overset{x}{xx}$ = P < 0·005, xx = P < 0·01, x = P < 0·025.

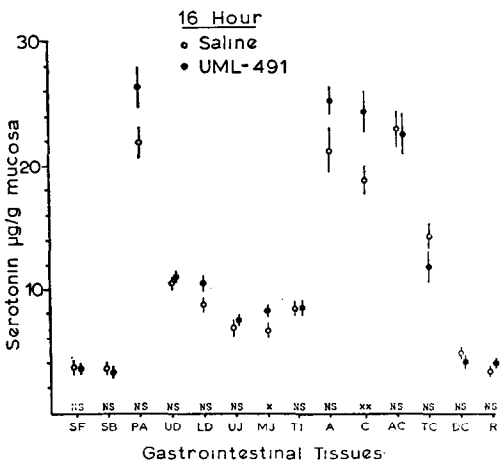

FIG. 3. Mean values ±1 S.E. for serotonin 16 hr after UML 491 or saline injections. Each point is the mean of 7–14 animals. P values are indicated: NS = not significant, xx = P < 0·01, x = P < 0.02. Abbreviations are given in Fig. 2.

The topographical distribution of serotonin throughout the bowel at the time of maximal response to UML 491 (1 hr), and after recovery (16 hr), as indicated in Fig. 1, is presented in Figs. 2 and 3. At 1 hr (Fig. 2), all tissues show an increased serotonin concentration compared to saline-injected control rats. However, in three of these areas (terminal ileum, appendix, and rectum) although the tissue serotonin concentrations are elevated, the differences between the drug-injected and the saline-injected groups are not significant, due to the small number of animals involved. In the remaining 11 bowel areas the differences are highly significant: $P < 0.001$ (stomach body, pyloric antrum, upper duodenum and jejunum, cecum, and ascending colon); $P < 0.005$ (stomach fundus, and mid-jejunum); $P < 0.01$ (descending colon); and $P < 0.025$ (lower duodenum and transverse colon). At 16 hr (Fig. 3), with the exception of the cecum ($P < 0.01$) and the mid-jejunum ($P < 0.02$), all tissues show comparable serotonin levels in the two groups.

From this short communication it is obvious that UML 491 has a pronounced effect on bowel serotonin. (Preliminary experiments have shown that UML 491 does not interfere with the actual determination of serotonin.) However, it is not possible to say whether the amine elevations noted result from an increase in the bound or free fractions. Certainly in brain, Freedman and Giarman[5] have shown that the increased levels of serotonin after LSD-25 result from greater amine binding. The physiological function of serotonin in the gastroduodenal area is not clear. UML 491 has been shown by Resnick *et al.*[12] to stimulate gastric secretion in man. Furthermore, this stimulatory effect is not abolished by vagotomy, which suggests the possibility of some local effect at the level of the parietal cell. In this regard it is of interest that serotonin has been shown to release histamine[13] and inhibit *N*-methyl transferase.[14]

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