COMPARATIVE STUDY ON THE SEROTONIN ANTAGONISM OF AMIDE DERIVATIVES OF LYSERGIC ACID AND OF ERGOT ALKALOIDS

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Among the substances with antagonistic effects against 5-hydroxytryptamine (5-HT, serotonin, enteramine) certain ergot derivatives play an important role. In 1953, Fingl and Gaddum showed that ergotamine and dihydroergotamine exert pronounced 5-HT antagonism. This property is even more specific in certain other tests than the adrenergic blocking action of these two alkaloids. An especially high antiserotonin activity was described for the diethylamide of lysergic acid (Gaddum, 1953) although this compound (LSD-25) is practically devoid of adrenergic blocking effects.

We have screened numerous derivatives of lysergic acid (Stoll and Hofmann, 1955) for their pharmacological properties. The present communication deals with comparative data on antiserotonin activity of more than forty "ergot derivatives", as determined on the isolated rat uterus. In addition to the natural and hydrogenated ergot alkaloids, about thirty semi-synthetic amide derivatives of lysergic acid were included in this investigation. *d*-Lysergic acid diethylamide (LSD-25) served as a reference standard throughout the study.

To test the degree of specificity of the 5-HT blocking effect, the acetylcholine antagonism of the different compounds was determined simultaneously on the rat uterus.

METHODS. The isolated rat uterus preparation was used as described by Gaddum and Hameed (1954) and according to previous experiments in our laboratory (Lanz, Cerletti and Rothlin, 1955). Virgin albino rats (Glaxo) weighing 180 to 200 gm. were injected the day prior to the experiment with 1 mgm./kgm. of stilbestrol, subcutaneously. The freshly excised uterine horns were suspended in an O_2-saturated bath of Jalon's solution (Gaddum, Peart and Vogt, 1949) kept at a constant temperature of 30°C.

Serotonin was applied at ten-minute intervals. After each contraction the preparation was washed for 30 seconds. In each case the optimal serotonin dose was first established and then maintained constant throughout the experiment. Within an average of two hours, constant responses were elicited and testing of inhibitory effects was begun. In all cases the antagonist (LSD-25 or the compounds to be compared with it) was in contact with the organ for 10 minutes. The doses necessary to produce a 50 per cent reduction of the next serotonin response were calculated according to the probit procedure. The relative activity of each compound was established by comparing it with LSD-25 (= 100 per cent). The values in tables 1 to 3 refer to this relative potency.

Acetylcholine antagonism was tested on the same organ which previously had served for determining the serotonin antagonism. From the doses necessary to produce 50 per cent inhibition of a submaximal serotonin and acetylcholine contraction, a ratio could be calculated indicating the more or less specific character of the antiserotonin effect.

RESULTS. 1. *LSD-25, isomers of LSD-25 and C_9,C_{10}-saturated LSD derivatives.* Figure 1 shows a typical example of effects obtained with increasing doses

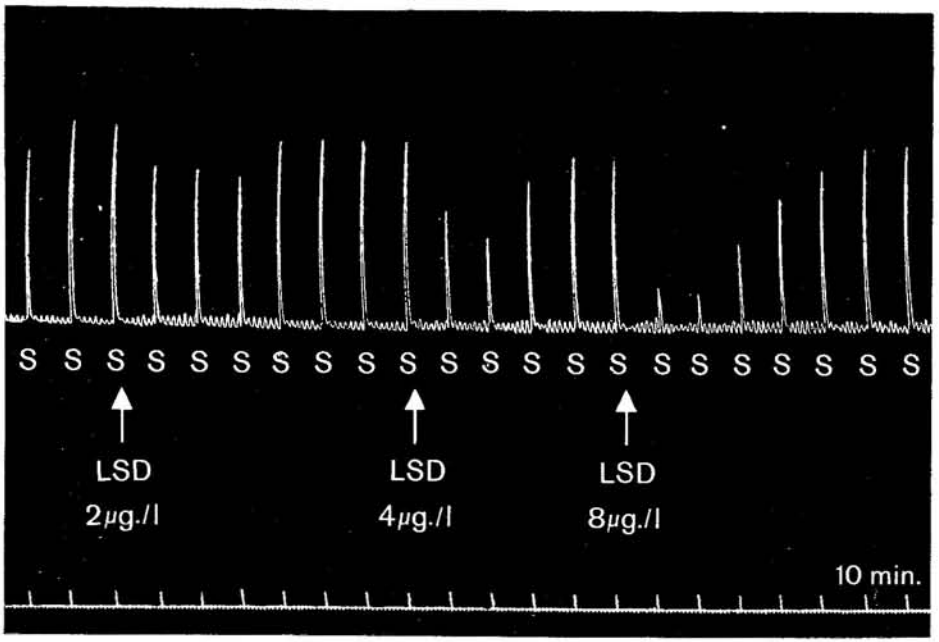


FIG. 1. Testing of serotonin inhibition by increasing doses of LSD on the isolated rat uterus.

The serotonin dose (10 microgm./l.) remains unchanged throughout the experiment. LSD is in contact with the muscle in each case only during 10 minutes.

of *d*-lysergic acid diethylamide (LSD-25). The degree of serotonin antagonism depends very much on the time during which the uterus is exposed to the influence of LSD (see part 8 under RESULTS). As already pointed out, our normal procedure is based on 10-minute intervals between subsequent serotonin effects. LSD is given immediately after the last control reaction of serotonin and washed out 10 minutes later with the next serotonin dose. Under these circumstances, the maximal LSD effect is usually observed only during the second application of serotonin, *i.e.* after 20 minutes. Recovery of the serotonin responses is rather slow. Depending on the dose of LSD employed, it takes from 40 to 90 minutes before normal serotonin contractions reoccur. LSD-25 by itself has no action on the uterus, at least not in the doses necessary to produce complete block of maximally active amounts of serotonin.

According to the molecular structure of lysergic acid, four isomers of LSD are possible. All four have been synthetized and tested. As shown in figure 2, the diethylamide of *l*-lysergic acid as well as the analogous derivatives of *d*- and *l*-isolysergic acid are practically ineffective, being about one thousand times weaker than LSD-25. By hydrogenation of the double bond between the carbon atoms 9 and 10, LSD loses about half of its antiserotonin activity. At the same time, the specificity of this dihydro-LSD, expressed by the ratios of serotonin and acetylcholine inhibition, is also decreased (table 4). Saturation of the same double

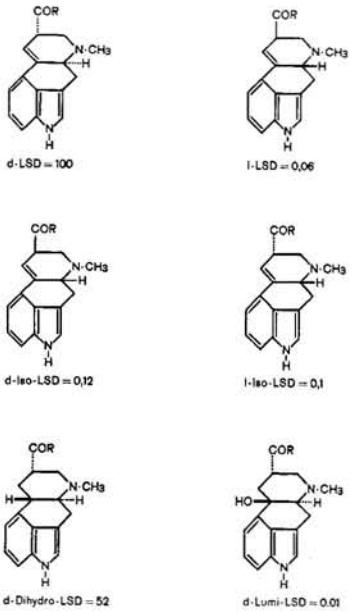


FIG. 2. Relative antiserotonin potency of LSD-isomers and C_9, C_{10}-saturated LSD-derivatives. R in the formulae = $—N(C_2H_5)_2$.

bond by one molecule of water under the influence of light yields the compound listed as Lumi-LSD (Stoll and Schlientz, 1955). In spite of its close resemblance to the hydrogenated LSD, Lumi-LSD is completely inactive.

2. *Disubstituted amide derivatives of d-lysergic acid.* Section A of table 1 summarizes the results obtained by a comparison of the unsubstituted and several disubstituted amides of *d*-lysergic acid. It shows that the antiserotonin activity of LSD is not reached by any of these compounds. It is, however, interesting to note that the affinity of the compounds to the uterine muscle, estimated from the effect of repeated washing of the preparation, continuously increases from the simple amide to the dibutylamide. This last compound produces a practically irreversible effect. Of the 5 disubstituted amides, LSD is not only the strongest but also the most specific as shown in figure 4 (see part 7 under RESULTS)

3. *Monosubstituted amide derivatives of lysergic acid.* In contrast to the data presented in the first part of table 1, the values for the relative antiserotonin potency of the monosubstituted lysergic acid amides seem to be related to the length of the alkyl rest, as shown in the second part (B) of table 1. Whereas the methylamide derivative is only slightly more effective than the simple lysergic acid amide, the activity increases subsequently with each lengthening of the side chain and reaches a fairly high value of 75 per cent in the case of *d*-lysergic acid amylamide. Qualitatively, all these monosubstituted compounds behave very similarly. They can easily be washed out and all exert their maximal effect on the first subsequent administration of serotonin, *i.e.* after 10 minutes. Recovery of the uterine response to serotonin is complete within 30 to 40 minutes.

Likewise, a more uniform pattern is found within this group when the ratio of serotonin and acetylcholine antagonism is tested (figure 4).

4. *Cyclic amide derivatives of lysergic acid.* The four compounds listed in section C of table 1 can be considered as having the two aminoethyl groups closed to form a five- or six-membered ring. Although some of the pharmacologic effects of LSD are enhanced by this ring formation (for example, the depressor effect of the pyrrolidide and pyrrolinide is stronger than with LSD (Cerletti, 1955), the antiserotonin activity is reduced ten to fifty times as compared with LSD.

5. *Ring-substituted LSD derivatives.* By substitution of different radicals, mainly in positions 1 and 2 of the ring complex of lysergic acid, new derivatives can be obtained, some of which are definitely superior to LSD as regards the inhibition of serotonin on the isolated rat uterus (table 2). The first of such compounds was the diethylamide of 2-bromo-*d*-lysergic acid, also known as BOL-148. In our earlier publications (Cerletti, 1956; Cerletti and Rothlin, 1955; Cerletti and Konzett, 1956) this compound was graded as one and one-half times stronger than LSD in tests on the isolated rat uterus. Many more experiments carried out since then have shown that the antiserotonin potency of BOL on the rat uterus on a weight per weight basis is not much higher. A significant difference between this compound and LSD could therefore not be confirmed. For this reason, BOL is listed in table 2 as identically active with LSD. There are, however, several other compounds showing about two to five times greater antiserotonin activity than LSD. 1-Acetyl-LSD is twice as potent as LSD if the compounds are compared according to our standard procedure, *i.e.* after having been in contact with the uterine muscle for a period of 10 minutes. In contrast to LSD, the antiserotonin effect of 1-acetyl-LSD does not increase with longer incubation periods (figure 6). This is, however, the case with 1-methyl-LSD which, on an average, is 3.7 times stronger than LSD. Figure 3 illustrates the effect of this compound in comparison to the effect of a double dose of LSD. So far the combined substitution of a methyl group and a bromine atom in positions 1 and 2, respectively, has yielded the most potent compound (MOB-61) with an activity 5.3 times that of LSD. Further studies with this interesting derivative are presently under way.

6. *Antiserotonin activity of natural and hydrogenated ergot alkaloids.* The diethylamide of lysergic acid belongs chemically to the ergonovine group or the group of similar semi-synthetic alkaloids with low molecular weight, for example methylergonovine. It seemed of interest to compare the antiserotonin effect of LSD with these substances. Fingl and Gaddum (1953) had found that dihydroergotamine was fairly active against serotonin. For this reason, we also included the whole group of the peptide alkaloids of ergot and their hydrogenated derivatives in our study. Table 3 summarizes our results. Even if corrections for the higher molecular weights were made, all the peptide alkaloids, with the exception of dihydroergotamine, show less than 10 per cent of the LSD activity. The alkaloids belonging to the "ergotoxine" group are characterized by the lack of a significant influence of hydrogenation on their antiserotonin activity. This is also true for ergonovine and methylergonovine. In contrast, both ergotamine

TABLE 1

Antiserotonin potency of 16 amide-derivatives of d-lysergic acid

Each compound has been tested in at least 8 experiments; in most cases, however, between 20 and 30 experiments were carried out.

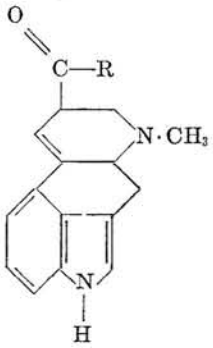
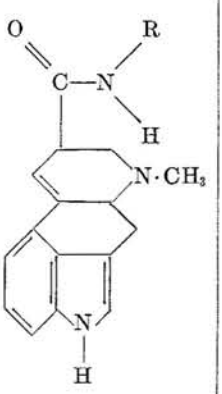
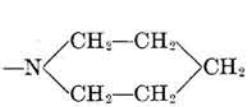
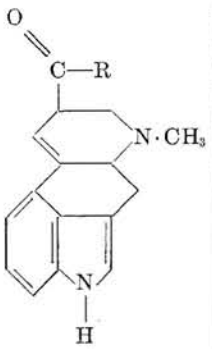
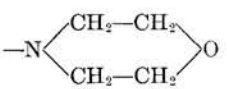
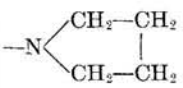
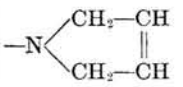
	R =	Name	Relative activity ± s.e.* (LSD = 100)
			%
A. Disubstituted amides	$-N(H)(H)$	*d*-lysergic acid amide	4.3 ± 0.5
	$-N(CH_3)(CH_3)$	*d*-lysergic acid dimethylamide	23.2 ± 1.3
	$-N(CH_2CH_3)(CH_2CH_3)$	*d*-lysergic acid diethylamide	100.0
	$-N(CH(CH_3)(CH_3))(CH(CH_3)(CH_3))$	*d*-lysergic acid diisopropylamide	23.2 ± 2.1
	$-N(CH_2CH_2CH_3)(CH_2CH_2CH_3)$	*d*-lysergic acid dipropylamide	42.3 ± 2.8
	$-N(CH_2CH_2CH_2CH_3)(CH_2CH_2CH_2CH_3)$	*d*-lysergic acid dibutylamide	31.2 ± 2.9
B. Monosubstituted amides	$-CH_3$	*d*-lysergic acid methylamide	6.3 ± 0.6
	$-CH_2CH_3$	*d*-lysergic acid ethylamide	11.9 ± 0.1
	$-CH(CH_3)(CH_3)$	*d*-lysergic acid isopropylamide	22.2 ± 2.4
	$-CH_2CH_2CH_3$	*d*-lysergic acid propylamide	40.0 ± 4.8
	$-CH_2CH_2CH_2CH_3$	*d*-lysergic acid butylamide	64.9 ± 6.1
	$-CH_2CH_2CH_2CH_2CH_3$	*d*-lysergic acid amylamide	75.1 ± 8.5

TABLE 1—*Continued*

	R =	Name	Relative activity ± s.e.* (LSD = 100)
			%
C. Cyclic amide, derivatives		*d*-lysergic acid piperidid	8.5 ± 1.6
		*d*-lysergic acid morpholid	2.0 ± 0.6
		*d*-lysergic acid pyrrolidid	4.7 ± 0.4
		*d*-lysergic acid pyrrolinid	4.1 ± 0.7

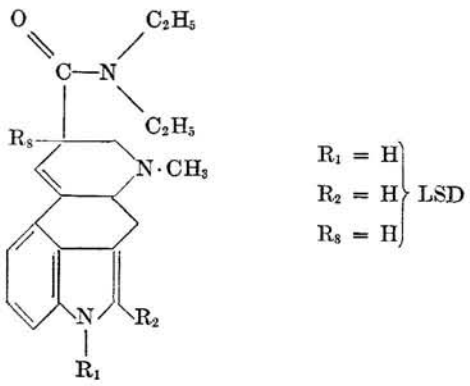
* s.e. = standard error.

and ergosine are rendered about two and one-half times more effective by conversion to their respective dihydro derivatives. As already mentioned above, hydrogenation of LSD results in a 50 per cent decrease of the antiserotonin potency. It is therefore quite clear that one and the same chemical alteration (saturation of one double bond) of the lysergic acid nucleus leads to absolutely opposite effects depending on the structural differences in the rest of the molecule (for example, the presence of pyruvic acid in ergotamine and ergosine and dimethylpyruvic acid in the three alkaloids, ergocornine, ergocristine and ergokryptine). From the point of view of qualitative characteristics, it must be mentioned that the peptide alkaloids in doses necessary to inhibit serotonin responses also produce more or less pronounced spontaneous contractions of the rat uterus. This is especially the case for the natural alkaloids and less so for the hydrogenated alkaloids. The antiserotonin effect of all these alkaloids develops rather slowly. In spite of several washings, the maximal inhibition is only seen after 30 to 60 minutes and the subsequent serotonin reactions show a relatively poor recovery.

As for the alkaloids of lower molecular weight, ergonovine was found to be quite an active antagonist of serotonin, being only 6 times weaker than LSD. In the publication by Gaddum *et al.* (1955) ergonovine (ergometrine) is mentioned as having no activity at all on the isolated rat uterus. This was probably due to a deteriorated sample of ergonovine, as mentioned in a more recent publication from the same laboratory (Savini, 1956). According to this paper, ergonovine proved to be only two to five times less active than LSD in antagonizing 5-HT on the isolated perfused vessels of the rabbit ear. For methylergonovine we found rather irregular results, but the activity was always higher than the one observed

TABLE 2

Antiserotonin potency of ring-substituted derivatives of LSD



Substitution	Name	Relative activity ± s.e.* (LSD = 100)
		%
$R_2 = H$, $R_8 = H$, $R_1 = COCH_3$	1-acetyl-LSD (ALD 52)	210 ± 21
$R_2 = H$, $R_8 = H$, $R_1 = CH_3O$	1-oxymethyl-LSD	58.9 ± 10.4
$R_2 = H$, $R_8 = H$, $R_1 = CH_3$	1-methyl-LSD (MLD 41)	368 ± 47
$R_2 = H$, $R_8 = H$, $R_1 = CONH$–(cyclohexyl)	1-carbanilido-LSD	7.6 ± 1.4
$R_1 = H$, $R_8 = H$, $R_2 = Br$	2-bromo-LSD (BOL 148)	103 ± 8.4
$R_1 = H$, $R_8 = H$, $R_2 = I$	2-iodo-LSD	57.4 ± 6.5
$R_1 = H$, $R_8 = H$, $R_2 = CH_2-N(CH_3)_2$	2-dimethylaminomethyl-LSD	18.5 ± 1.8
$R_1 = H$, $R_2 = H$, $R_8 = CH_3$	8-methyl-LSD	15.8 ± 2
$R_1 = CH_3$, $R_2 = Br$, $R_8 = H$	1-methyl-2-bromo-LSD (MOB 61)	533 ± 35

* s.e. = standard error

with ergonovine. On an average, methylergonovine is about three and one-half times more effective than ergonovine. Both alkaloids fully inhibit the serotonin effect without themselves stimulating the uterus as was frequently the case with the peptide alkaloids. Hydrogenation of ergonovine and methylergonovine hardly changes the antiserotonin property of the two compounds.

7. *Specificity of the antiserotonin effect of LSD and related substances.* An index of specificity was obtained by comparing the doses necessary for acetylcholine and serotonin inhibition. The ratios ED_{50} antiacetylcholine:ED_{50} antiserotonin for several compounds are listed in table 4. For LSD a value of more than five thousand could be established. This means that for a 50 per cent inhibition of a

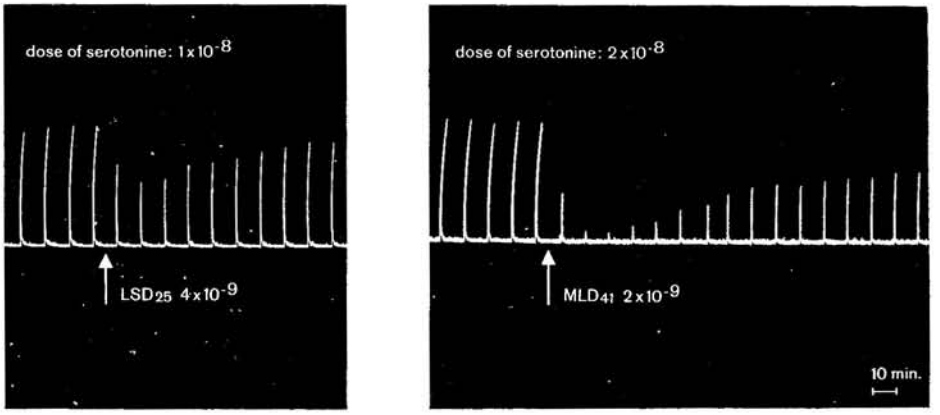


FIG. 3. Comparison of serotonin-inhibition on the isolated rat uterus by LSD 25 and 1-methyl-lysergic acid diethylamide (MLD 41).

A stronger and longer lasting effect is produced by one-half of the dose of MLD 41 as compared with LSD 25.

submaximal contraction induced by acetylcholine a more than five thousand times larger amount of LSD is needed than for a 50 per cent inhibition of an identical serotonin effect. Within the series of mono- and disubstituted amides of lysergic acid, LSD is likewise superior from this point of view to all the other compounds (see figure 4). It is also interesting to note that BOL-148, although as active as LSD from a quantitative point of view, has a much lower specificity index (table 4). An even lower value is found for dihydroergotamine, whereas ergonovine and methylergonovine have high indices. Only one compound reaches

TABLE 3

Antiserotonin potency of natural and hydrogenated ergot alkaloids

Group		Name	Relative activity ± s.e.* (LSD = 100)
			%
Peptide alkaloids	Ergotamine group	Ergotamine	4.3 ± 0.5
		Dihydroergotamine	11.1 ± 1.7
		Ergosine	3.4 ± 0.4
		Dihydroergosine	8.2 ± 0.8
	Ergotoxine group	Ergocornine	4.3 ± 0.5
		Dihydroergocornine	4.1 ± 0.2
		Ergocristine	1.7 ± 0.2
		Dihydroergocristine	1.5 ± 0.6
		Ergokryptine	1.8 ± 0.2
		Dihydroergokryptine	1.6 ± 0.4
	Ergonovine group	Ergonovine	17.0 ± 3.1
		Dihydroergonovine	19.7 ± 2.2
		Methylergonovine	61.4 ± 14.4
		Dihydromethylergonovine	58.1 ± 6.3

* s.e. = standard error.

TABLE 4

Specificity of the antiserotonin effect of LSD and related substances as illustrated by comparison of doses required for acetylcholine and serotonin antagonism

Group	Name	Number of experiments	Specificity index: $\frac{ED_{50}\text{ antiacetylcholine}}{ED_{50}\text{ antiserotonin}}$
I	dihydro-lysergic acid diethylamide	4	1137 ± 290 s.e.*
II	*d*-lysergic acid amide	3	409 ± 259
	d-lysergic acid dimethylamide	3	1804 ± 95
	d-lysergic acid diethylamide	12	5236 ± 1189
	d-lysergic acid dipropylamide	3	343 ± 83
	d-lysergic acid dibutylamide	2	30 ± 4.6
III	*d*-lysergic acid amide	3	409 ± 259
	d-lysergic acid methylamide	4	270 ± 62
	d-lysergic acid ethylamide	4	425 ± 56
	d-lysergic acid propylamide	4	485 ± 94
	d-lysergic acid butylamide	4	402 ± 131
IV	1-acetyl-lysergic acid diethylamide	11	1345 ± 322
	1-methyl-lysergic acid diethylamide	9	2855 ± 608
	2-bromo-lysergic acid diethylamide	13	908 ± 324
	1-methyl-2-bromo-lysergic acid diethylamide	4	5960 ± 960
V	dihydroergotamine	3	291 ± 45
	ergonovine	12	3547 ± 793
	methylergonovine	5	3164 ± 654

* s.e. = standard error.

a value even higher than LSD, and that is the methyl- and bromo-substituted derivative MOB-61 which quantitatively is the most potent substance we have found to date.

8. *Relationship between the degree of serotonin antagonism and the exposure time to the inhibitory substance.* As first described by Gaddum *et al.* (1955), the intensity of the serotonin block produced by LSD increases with the time during which the uterus stays in contact with the inhibitor. This behavior has also been tested for the most potent derivatives of LSD using the following procedure (figure 5): First, a dose response curve for serotonin is established; subsequently the inhibitor is added, but not only to the solution present in the bath but also to the stock of wash solution. In this way, a constant concentration of the inhibitor can be maintained in the bath for any desirable time in spite of the repeated administration of serotonin every ten minutes. As shown in figure 5a, the continuous presence of the inhibitor (LSD) in the bath necessitates continuously increasing amounts of serotonin to reproduce the former degree of contraction. When plotting the ratios of serotonin doses before (S_2) and after addition (S_1) of the inhibitor ($S_1:S_2$) against the time during which the inhibitor is present in the bath, the curves presented in figure 6 are obtained. They show that BOL-148 behaves very much like LSD, whereas the 1-methyl and the 1-methyl-2-bromo derivative show an even more pronounced increase of the ratio

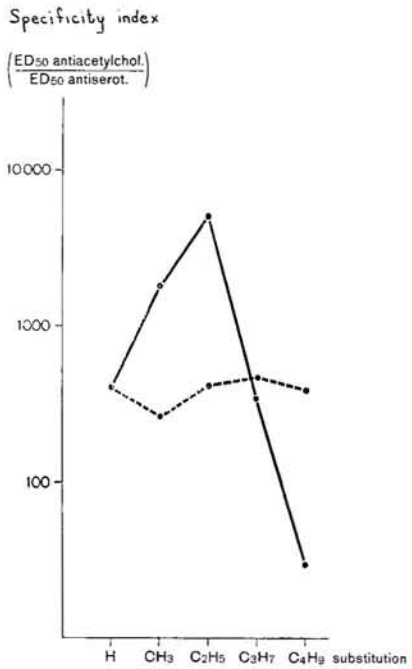


FIG. 4. Relationship between chemical constitution and specificity of the antiserotonin effect of lysergic acid amide derivatives.

• ———— • = Disubstituted compounds. • - - - - - - - - • = Monosubstituted compounds.

S_1:S_2 than LSD. Quite in contrast to this behavior, the 1-acetyl derivative of LSD reaches the maximum effect within a relatively short period of time without further increase of the serotonin ratio. This is also found in the experiments with ergonovine, an example of which is shown in figure 5b. Considering this difference between ergonovine on one side and LSD on the other, it seems as if the reaction of the LSD-like substances with the serotonin receptors is not completed by the first contact but is a continuing process getting less and less reversible. In the case of ergonovine and acetyl-LSD, the interaction of the inhibitor with the serotonin receptors develops to a maximum already within ten to twenty minutes and subsequently remains in a steady state which is more easily reversible than in the case of LSD.

DISCUSSION. The antagonism exerted by the hallucinogenic drug LSD on different effects of serotonin has aroused much interest since serotonin is present in the brain stem, mainly in the hypothalamus. Comparatively little is known about the effect on man of many of the derivatives described in this paper. There is undoubtedly no direct relationship between the peripheral antiserotonin action on smooth muscles and the effects on the central nervous system. In any case, the fact remains that LSD is the most active and also the most specific serotonin inhibitor within a large group of several amide derivatives of lysergic acid. The few compounds exceeding LSD in antiserotonin action all possess a diethylamino side chain, and the increased activity is obtained by

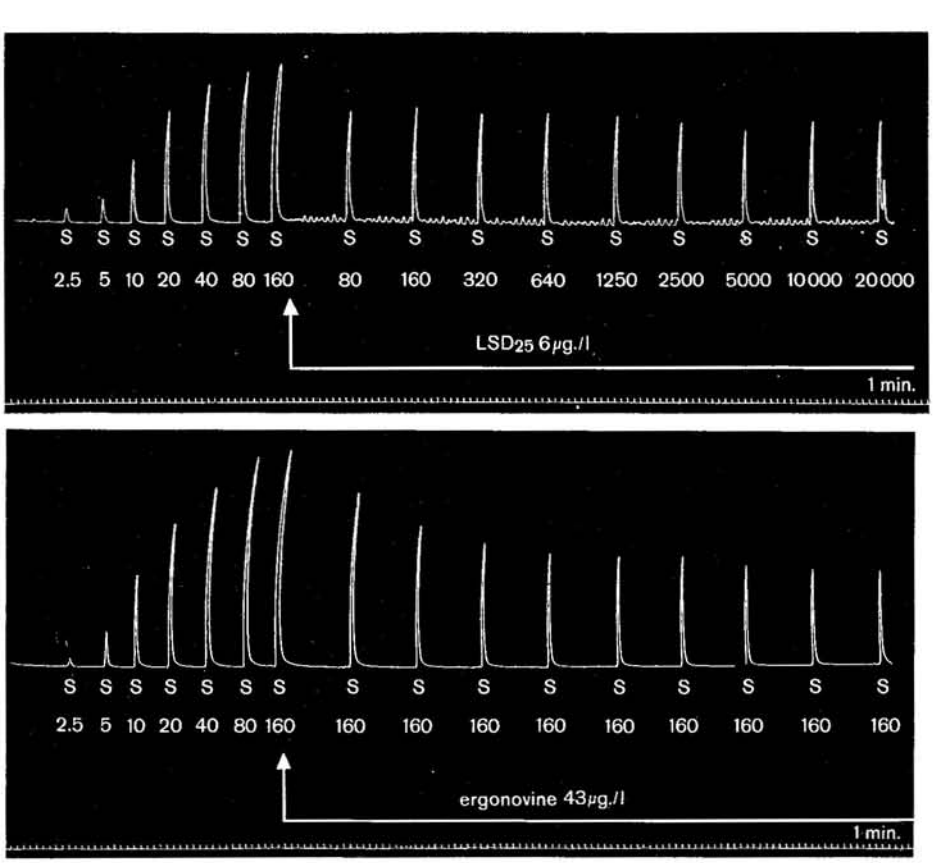


FIG. 5. Effect of incubating the rat uterus over a longer period of time with LSD and ergonovine.

S = serotonin; each figure under "S" indicates the dose of serotonin in micrograms per liter. After establishing a dose-response curve, the inhibitor (LSD in figure 5a and ergonovine in figure 5b) is applied at the time indicated by the arrow. The inhibitor is added in the same concentration also to the wash solution and thus will not be removed from the bath by washing the subsequent serotonin dose as in the usual procedure exemplified in figure 1 and figure 3. a) (upper half). Due to the continuous presence of a constant amount of LSD in the bath increasing quantities of serotonin are needed to overcome the inhibitory effect of LSD. If 10 minutes after LSD four times more serotonin (80 instead of 20 microgm./liter) is sufficient to reproduce the original size contraction, the dose must be increased 32 times after 40 minutes and 500 times (10,000 microgm./liter) after 80 minutes to accomplish the same purpose. b) (lower half). Using erogonovine instead of LSD for an otherwise identical experiment, it is noted that with a relatively slight increase of the serotonin dose the inhibitory effect is overcome and a steady state is reached in a rather short time.

certain substitutions on the ring complex. From purely pharmacologic findings it is not predictable whether substances like the 1-acetyl, 1-methyl and 1-methyl-2-bromo derivatives are hallucinogenic. Occasional observations in our laboratory would suggest that acetyl-LSD can produce psychic alterations, but this still has to be confirmed by clinical trial of this and the other derivatives. Several

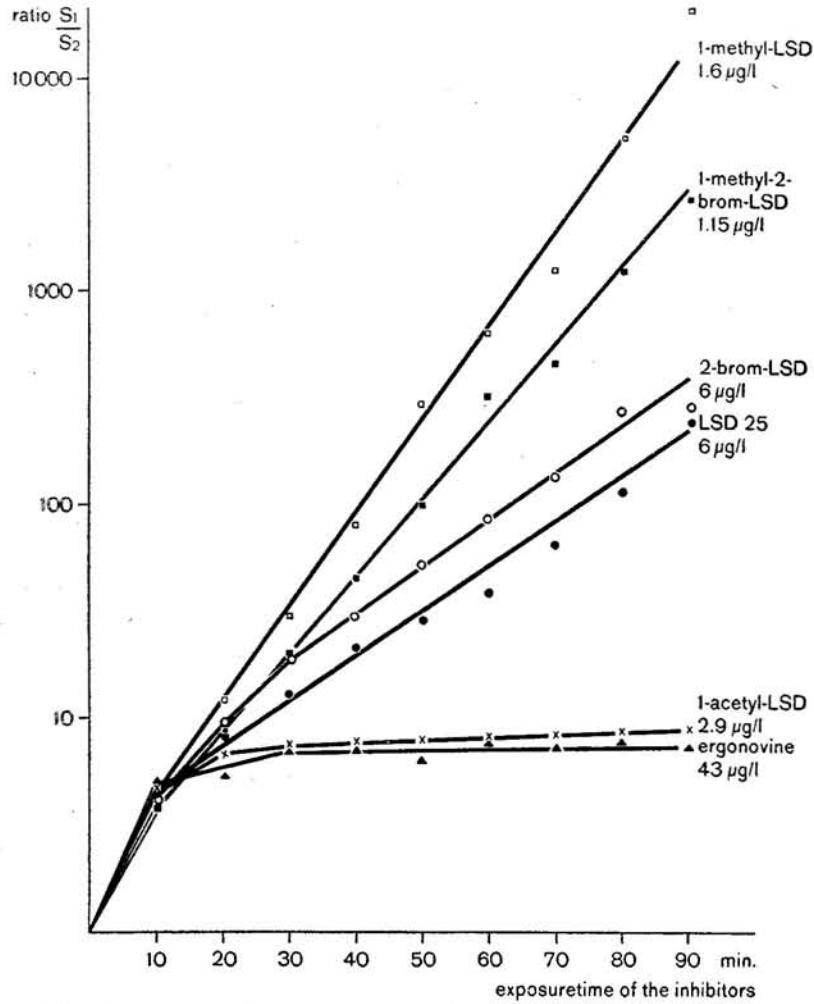


FIG. 6. Graphic presentation of the relationship between the dose ratio S_1:S_2 and the exposure time of the inhibitor.

The doses of the different antagonists were selected to give a more or less similar degree of serotonin inhibition within the first ten minutes. S_1 and S_2 are doses of serotonin before (S_2) and at different times after (S_1) administration of the inhibitor, and it can be seen that the ratio S_1:S_2 increases continuously in the case of several compounds whereas in others it remains nearly constant.

other pharmacologic properties of LSD are not shared to the same degree by the above mentioned potent antiserotonin compounds. For example, 1-acetyl-LSD is seven to eight times and 1-methyl-LSD more than twenty times less pyretogenic in the rabbit than LSD. On the other hand, 200 times less 1-methyl-LSD than LSD is sufficient to completely inhibit the serotonin-induced barbiturate potentiation in mice (unpublished data). It may be hoped that the comparative analysis of the effects in animals and in man of the potent serotonin inhibitors among the LSD derivatives will contribute to the understanding of the still

complex question of a possible interaction of LSD and serotonin in the central nervous system. It has recently been claimed that LSD is primarily not an inhibitor of serotonin but potentiates the serotonin contractions of the rat uterus in the smallest effective doses (Costa, 1956; Delay and Thuillier, 1956). We were not able to confirm such a dual effect of LSD. When using smaller doses than the minimal ones required for a partial serotonin block, a significantly increased response to serotonin was not observed. Actually 48 tests in 14 different organs were carried out in the dose range 5×10^{-10} to 1×10^{-12} to obtain evidence for a potentiating effect. In only 3 of these 48 tests was a slight increase of the response to serotonin noted. We would, therefore, hesitate to attribute to such an exceptional and not reproducible effect an importance similar to the clear-cut antagonism between LSD and serotonin. A significant potentiation of serotonin was also not found for any of the LSD derivatives.

SUMMARY

The quantitative and qualitative characteristics of the 5-HT antagonism of a large number of natural and semi-synthetic "ergot derivatives" have been studied on the isolated rat uterus. Within a group of about twenty amide derivatives of lysergic acid, more or less closely related to LSD-25 from a chemical point of view, none reached the degree of activity and specificity of this well known serotonin inhibitor. The substance next to LSD in antiserotonin potency was the mono-amylamide of lysergic acid. Three stereoisomers of LSD were practically ineffective. This was also true for Lumi-LSD, whereas dihydro-LSD still maintained 50 per cent of the activity of the unsaturated original product. Similar comparative studies with the whole series of natural ergot alkaloids and their respective hydrogenated derivatives revealed only moderate degrees of serotonin antagonism. The semi-synthetic alkaloid methylergonovine, however, proved to be quite an effective and specific inhibitor. Substances with antiserotonin activities higher than LSD were found within a group of LSD derivatives with different substitutions on the ring structure of lysergic acid. The most potent compound thus far studied was the 1-methyl-2-bromo lysergic acid diethylamide.

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