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Specificity of the Antibody Receptor Site to D-Lysergamide: Model of a Physiological Receptor for Lysergic Acid Diethylamide

(molecular structure/hallucinogenic/rabbit/guinea pig/psychotomimetic)

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ABSTRACT **Antibodies to D-lysergic acid have been produced in rabbits and guinea pigs and a radioimmunoassay for the hapten was developed. The specificity of this lysergamide–antilysergamide reaction was determined by competitive binding with unlabeled lysergic acid diethylamide (LSD), psychotomimetic drugs, neurotransmitters, and other compounds with diverse structures. LSD and several related ergot alkaloids were potent competitors, three to seven times more potent than lysergic acid itself. The *N,N*-dimethyl derivatives of several compounds, including tryptamine, 5-hydroxytryptamine, 4-hydroxytryptamine, 5-methoxytryptamine, tyramine, and mescaline, were only about ten times less effective than lysergic acid, even though these compounds lack some of the ring systems of lysergic acid. The pattern of inhibition by related compounds with various substituents suggests that the antibody receptor site recognizes structural features resembling the LSD molecule. In particular, the aromatic nucleus and the dimethylated ethylamine side chain in phenylethylamine and tryptamine derivatives may assume in solution a conformation resembling ring A and the methylated nitrogen in ring C of LSD. Among the tryptamine derivatives, a large percentage of the most potent competitors are also psychotomimetic compounds.**

LSD (*N,N*-diethyl-D-lysergamide), psilocin, and mescaline are hallucinogenic compounds and, despite considerable differences in their structures, show cross tolerance, suggesting that their behavioral effects may be mediated at similar sites in the central nervous system, perhaps at a common set of postsynaptic receptors (1–3). Several investigators have used molecular orbital calculations and/or steric models to describe the common structural features responsible for the similar psychotomimetic activities of these compounds (4–11).

When we reported the specificities of the antibodies to 2,5-dimethoxy-4-methylamphetamine, mescaline, and 3,4-dimethoxyphenylethylamine, we suggested that antibodies to LSD might reveal similarities in conformation among structurally dissimilar psychotomimetic compounds (12). We described in this paper the production and serologic characterization of such antibodies. The antibodies to the lysergamide moiety bind hallucinogenic drugs and related compounds of the tryptamine, phenylethylamine, and phenylisopropylamine families.

MATERIALS AND METHODS

Most of the chemicals used in this study were from commercial sources. 3-methoxyphenylethylamine, 3,5-dimethoxyphenylethylamine, *N*-methyl-3,4,5-trimethoxyphenylethylamine, and *N,N*-dimethyl-3,4,5-trimethoxyphenylethylamine were the generous gifts of Dr. W. E. Scott of Hoffmann-La Roche. DOM (2,5-dimethoxy-4-methylamphetamine) was given to us by Dr. S. H. Snyder of Johns Hopkins University. Sandoz Pharmaceuticals provided us with ergonovine, methylergonovine, ergosine, and ergotomine. LSD tartarate powder (Sandoz Batch no. 98601) and psilocybin powder (Sandoz Batch no. 55001) were provided by the U.S. Food and Drug Administration and the National Institute of Mental Health.

Psilocin was obtained by dephosphorylating psilocybin with alkaline phosphatase (13). To 140 μg of psilocybin in 0.6 ml of 0.05 M Tris buffer, pH 8.0, were added 20 μl of bacterial alkaline phosphatase (10 mg/ml, 38.5 units/mg from Worthington). After incubation at room temperature for 10 min, aliquots were withdrawn and assayed immediately in the binding assay. Further incubation with enzyme (up to 2 hr) did not alter the inhibitory effectiveness, indicating that the dephosphorylation was complete in 10 min.

D-Lysergic acid was coupled by its carboxyl group to the ε-amino groups of poly(L-lysine) (molecular weight 95,000) with the use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (14). This dehydration reaction resulted in the formation of an amide bond between the reactive groups to give a poly(L-lysine)–lysergamide conjugate. In a representative synthesis, 30 mg of lysergic acid in 1.5 ml of pyridine and 30 mg of poly(L-lysine) in 1.5 ml of water were mixed and the pH was adjusted to 7.0–7.6. 60 mg of the carbodiimide was added, and the reaction mixture (under nitrogen) was left at 25°C overnight. It was then dialyzed exhaustively against 0.15 M NaCl–5 mM phosphate buffer, pH 7.0. The extent of substitution, estimated from spectral measurements, indicated that the molar ratio of coupled lysergic acid to lysine ranged from 1:6 to 1:10. A synthesis similar to the above was performed with the copolymer poly-(L-Glu^{36}, L-Lys^{24}, L-Ala^{35}, L-Tyr^{5}) in order to obtain a conjugate that could be labeled with ^{125}I (15–17). A modification of the electrolytic iodination technique outlined by Rosa *et al.* (18) was used. The reaction mixture, containing 25 μg of conjugate and 3 mCi of Na^{125}I in 1 ml of 0.9% NaCl, was exposed to a current of 2–5 μA for 10–15 min. Free ^{125}I was removed by dialysis. The specific activity was approximately 10 μCi of ^{125}I/μg of conjugate.

For immunization, 1 mg of the polylysine–lysergamide conjugate was complexed to 300 μg of succinylated hemocyanin in a volume of 1 ml. The resulting flocculent suspension was emulsified with an equal volume of complete Freund's

Abbreviation: LSD, *N,N*-diethyl-D-lysergamide.

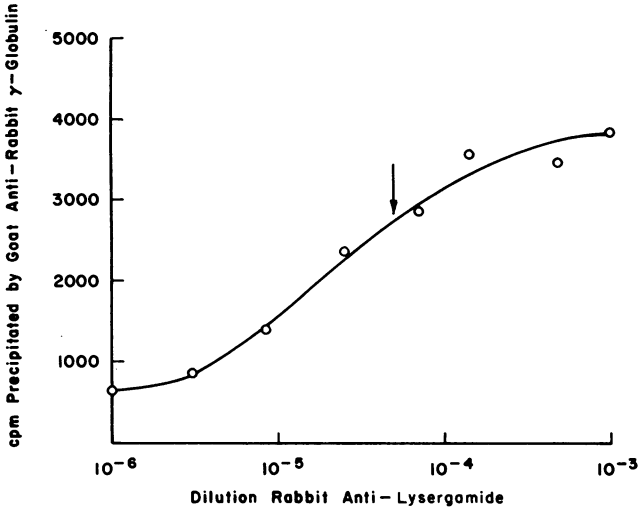

FIG. 1. Binding of ^{125}I-labeled copolymer–lysergamide by anti-polylysine–lysergamide. ^{125}I-labeled copolymer–lysergamide (6400 cpm) was incubated for 60 min at 37°C with various dilutions of antiserum in a volume of 1.2 ml (0.01 M Tris·HCl, pH 7.5, 0.14 M NaCl, 0.1% gelatin). After addition of carrier γ-globulin (normal rabbit serum, 0.1 ml of a 1/100 dilution), 0.1 ml of undiluted goat anti-rabbit γ-globulin was added and the reaction mixture was incubated overnight at 2–4°C. After centrifugation, the immune precipitate containing ^{125}I-labeled copolymer–lysergamide was counted in a Packard auto-gamma spectrometer. 600 cpm were precipitated in the absence of immune serum.

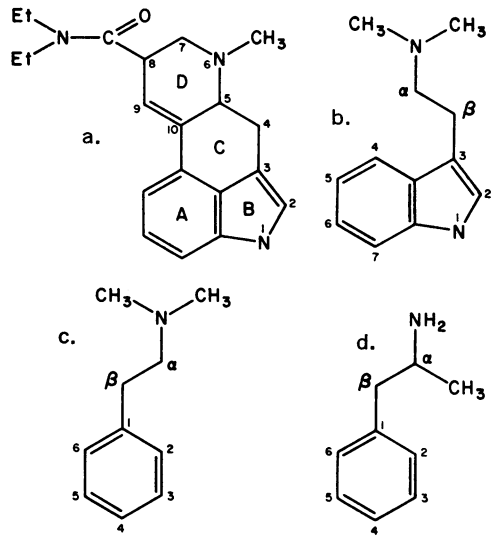

FIG. 3. Possible structural similarities among (*a*) LSD; (*b*) tryptamine derivatives (e.g., *N,N*-dimethyltryptamine); (*c*) phenylethylamine derivatives [e.g., 4-OH-*N,N*-dimethylphenylethylamine (hordenine)] and 3,4,5-trimethoxyphenylethylamine (mescaline); (*d*) and phenylisopropylamine derivatives (e.g., amphetamine).

adjuvant. 1 ml was injected into the toepads and leg muscles of each of two rabbits and five guinea pigs. 3 weeks later the animals were bled. This schedule of immunization was repeated with the rabbits every 6 weeks.

RESULTS AND DISCUSSION

All seven animals immunized with the polylysine–lysergamide conjugate (complexed to succinylated hemocyanin) produced complement-fixing antibodies when tested with the conjugate. Polylysine, alone or treated with carbodiimide, was serologically inert. The complement-fixing activity of the antisera increased with time of immunization. For example, no complement-fixing activity was found in the rabbit sera obtained prior to immunization or 1 week after the initial injection. In the second and third weeks after immunization, the complement-fixing titers of the antisera were 150 and 3000 for the first rabbit and 100 and 2000 for the second rabbit. 2 weeks after a single booster injection, the complement-fixing titer of each of the two antisera was 1:5,000 and 1:12,000, respectively. The guinea pig sera also showed increased serological activities with time of immunization. After gel filtration in Sephadex G-200, the antibodies to the hapten were found in the 7S γ IgG fraction of the rabbit sera.

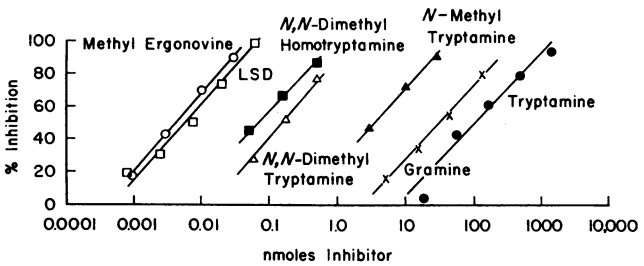

FIG. 2. Inhibition of binding in the ^{125}I-labeled copolymer–lysergamide anti-polylysine–lysergamide reaction by lysergamide and indoleamine derivatives. Reaction conditions are the same as those used for binding (Fig. 1), except that increments of each inhibitor were added at zero time and allowed to compete with the ^{125}I-labeled copolymer–lysergamide (6400 cpm) for the antibody (present at a final dilution of 1/30,000).

The data in Fig. 1 illustrate the binding of the ^{125}I-labeled copolymer–lysergamide conjugate by one of the rabbit antisera. An increase in binding activity was observed as immunization progressed. Although the competition data reported in this paper were obtained with antiserum from a single rabbit, the antisera of the second rabbit and the guinea pigs gave qualitatively similar results. For competitive binding experiments, the antiserum was used at a final dilution of 1/30,000 (the arrow in Fig. 1). The data in Fig. 2 illustrate the dose–response curves of several inhibitors. As little as 1 pmol of LSD can be detected by these assays.

D-Lysergic acid, LSD, and the ergot alkaloids are potent inhibitors of the antigen–antibody reaction (Table 1*A*). The lysergamide moiety, with its four rings and N^6-methyl group, is common to all these compounds (Fig. 3*a*) suggesting that the antibody recognizes these structures. LSD and the ergot alkaloids are somewhat more potent inhibitors than lysergic acid, probably because they, like the conjugate used for immunization, contain an amide bond. Large variations in the size of amide-group substituents do not markedly change their inhibitory capacity. Ergotamine contains an amide substituent that has a molecular weight five times that of the diethylamide group of LSD, yet the compounds inhibit the antigen–antibody reaction at about the same concentration.

Several compounds whose structures differ appreciably from that of LSD are also strong inhibitors of the antigen–antibody reaction. The *N,N*-dimethylated derivatives of

tryptamine, 5-hydroxytryptamine, 5-methoxytryptamine, and 4-hydroxytryptamine, for example, lack the C and D rings of LSD (Fig. 3) and also contain substituents on the indole ring. Nevertheless, they are only about 30 times less inhibitory than LSD (Table 1*B*) and 150–800 times more effective than their corresponding free amines. The corresponding amino acids are not inhibitory at concentrations a thousandfold greater.

From this and other examples (Table 1*C*), it is evident that methylation of the amino group substantially alters inhibitory potency. In general, monomethylation of the free amine has a much smaller effect than dimethylation of the free amine. *N,N*-dimethyltryptamine is 13 times more effective than *N*-methyltryptamine and 500 times more effective than tryptamine itself. *N,N*-dimethylmescaline is about 20 times less active than LSD, 17 times more active than *N*-methylmescaline, and 130 times more active than mescaline. *N,N*-dimethyltyramine is approximately 700 times more inhibitory than tyramine.

Other substitutions on the amino nitrogen produce different results. The inhibitory effectiveness of *N,N*-diethyltryptamine is only about one-sixth that of *N,N*-dimethyltryptamine (Table 1*B*). Substitution with an acetyl group, as in *N*-acetylserotonin and *N*-acetyl-5-methoxytryptamine, yields compounds that are not inhibitory even at a concentration of 200 nmol/1.2 ml.

While about 20 nmol of psilocybin (*O*-phosphoryl-4-OH-*N,N*-dimethyltryptamine) is required to inhibit the antigen–antibody reaction, only 0.16 nmol of psilocin (the dephosphorylated derivative) gives an equivalent amount of inhibition. Psilocybin is rapidly dephosphorylated in the rat both *in vitro* and *in vivo*, suggesting that psilocin is the active form of this compound (19). Using the space-filling Courtauld Atomic Models and orienting the indole group with rings A and B of LSD, we find that the phosphate group on the 4 position of psilocybin prevents the dimethylated side-chain nitrogen from approximating the spatial relationship that the methylated N^6 bears to ring A of LSD. [The configuration of our LSD model is that of biologically active LSD (20) and the orientation of the electron-dense center at N^6 follows the argument of Kang and Green (10); that is, the lone pair N^6 electrons are below the plane of LSD in Fig. 3*a*, whereas the amide group is above the plane.] The hydroxyl group in psilocin, by contrast, does permit the freely rotating *N,N*-dimethylated side chain to be oriented to resemble LSD without undue strain on any bond. (The question of whether the charged or uncharged form of LSD binds to the antibody receptor site cannot be answered at this time. Studies have yet to be carried out over a range of hydrogen ion concentrations.)

The length of the side chain on the indole nucleus (Table 2*A*) is also important. Gramine has one less side-chain carbon than does *N,N*-dimethyltryptamine and is 100 times less effective as an inhibitor; *N,N*-dimethylhomotryptamine has one more side chain carbon than *N,N*-dimethyltryptamine and is as effective as *N,N*-dimethyltryptamine. By orienting the aromatic nucleus and the amino nitrogen of a Courtauld model of *N,N*-dimethyltryptamine to approximate the LSD structure (which is fixed by virtue of the ring system), we find that the interatomic distance between C^4 and the amino nitrogen of *N,N*-dimethyltryptamine differs from the C^{11} to N^6 distance of LSD by no more than about 0.2 Å. The C^4–amino nitrogen distance in *N,N*-dimethylhomotryptamine can be surprisingly similar to the corresponding distance in *N,N*-dimethyltryptamine, but the corresponding measurement in gramine is approximately 1.0 Å less. The difference in degree of inhibition could be explained on this basis.

TABLE 1. *Inhibition of the lysergamide antigen–antibody reaction*

Compound	nmol required for 50% inhibition
A. By lysergic acid derivatives	
D-Lysergic acid	0.023
N,N-diethyl-D-lysergamide (LSD)	0.0068
Ergonovine	0.0031
Methylergonovine	0.0041
Ergosine	0.0036
Ergotamine	0.0050
B. By N-substituted tryptamine derivatives	
Tryptamine	101.0
N-methyltryptamine	2.6
N,N-dimethyltryptamine	0.19
N,N-diethyltryptamine	1.3
5-OH-tryptamine (serotonin)	24.2
5-OH-*N,N*-dimethyltryptamine (bufotenine)	0.20
5-OH-*N*-acetyltryptamine (*N*-acetylserotonin)	>200*
5-methoxytryptamine	10.0
5-methoxy-*N,N*-dimethyltryptamine	0.18
5-methoxy-*N*-acetyltryptamine (melatonin)	>200*
O-phosphoryl 4-OH-*N,N*-dimethyltryptamine (psilocybin)	23.0
4-OH-*N,N*-dimethyltryptamine (psilocin)	0.16
C. By N-substituted phenylethylamine derivatives	
4-OH phenylethylamine (tyramine)	105.0
N,N-dimethyltyramine	0.19
3,4,5-trimethoxyphenylethylamine (mescaline)	20.2
N-methylmescaline	2.5
N,N-dimethylmescaline	0.15

* No inhibition observed at this concentration. Assay conditions were the same as those described in the legends of Figs. 1 and 2.

The phenylisopropylamines, with the methyl group on the α-carbon and an unsubstituted amino group, are effective competitors at about 20 nmol/1.2 ml, a value not appreciably affected by substituents in the aromatic nucleus; amphetamine, DOM, and α-methyl-dopamine are equally effective (Table 2*B*). Ephedrine, which unlike the other compounds has an *N*-methyl group, is seven times more effective a competitor than amphetamine.

Among the phenylethylamine compounds containing a free amino group, the parent compound and the derivatives with a single hydroxyl or methoxy group in the *meta* or *para* position give 50% inhibition of the antigen–antibody reaction at concentrations of 100–200 nmol/1.2 ml (Table 2*C*). The disubstituted and trisubstituted derivatives are inhibitory at 10–30 nmol/1.2 ml. The ring substituents decrease the similarity of phenylethylamine to LSD, and therefore might be expected to reduce the inhibitory potency of phenylethylamine; on the contrary, single substituents do not appreciably alter the inhibitory potency and di- and trisubstitutions markedly increase it, indicating that the antibody does not recognize this portion of the molecule. A possible explanation

TABLE 2. *Inhibition of the lysergamide antigen–antibody reaction*

Compound	Substituents	nmol required for 50% inhibition
A. Inhibition by N,N-dimethylated indole compounds having side chains of different lengths		
3-(*N,N*-dimethylaminomethyl)indole (gramine)		20.0
5-methoxygramine		16.0
N,N-dimethylhomotryptamine		0.10
B. Inhibition by phenylisopropylamine derivatives		
dl-amphetamine		18
2,5-dimethoxy-4-methylphenylisopropylamine (DOM)		18
α-methyl dopamine		20
N-methyl-β-OH-phenylisopropylamine (ephedrine)		2.5
C. Inhibition by phenylethylamine derivatives containing a free amino group and substituents on the aromatic nucleus		
Phenylethylamine	0	130
4-OH-phenylethylamine (tyramine)	1	105
4-methoxyphenylethylamine	1	200
3-methoxyphenylethylamine	1	150
3-methoxy-4-hydroxyphenylethylamine	2	30
3,4-dimethoxyphenylethylamine	2	11
3,5-dimethoxyphenylethylamine	2	20
3,4-dihydroxyphenylethylamine (dopamine)	2	18
3,4,5-trimethoxyphenylethylamine (mescaline)	3	20.2

TABLE 3. *Inhibition of the lysergamide antigen–antibody reaction*

	nmol required for 50% inhibition
A. Compound	
L-epinephrine	130
L-norepinephrine	110
DL-metanephrine	18
DL-normetanephrine	46
Harmaline	8
Yohimbine	260
N,N-dimethylethylamine	400
N-α-dimethylcyclohexanethylamine	500

B. The following compounds did not inhibit at the concentrations listed (per 1.2 ml):

At 50 nmol	At 1000 nmol
Adrenochrome	4-OH-phenylacetic acid
3-indoleacetic acid	3,4-dimethoxyphenylacetic acid
5-OH-indole	3-methoxy-4-OH-phenylacetic acid
At 200 nmol	3-OH-phenylethylglycol
L-phenylalanine	3-4-dihydroxyphenylethylglycol
L-tyrosine	Vanillin
L- or DL-3,4-dihydroxyphenylalanine (Dopa)	Resorcinol
L-tryptophan	Hydroquinone
L-, DL- or D-5-OH-tryptophan	Catechol
Homovanillic acid	Putrescine
DL-3-methoxy-4-OH-mandelic acid	Niacin
Colchicine	Nicotinamide
Spermidine	L-serine
	L-glutamic acid
	Histamine
	5-OH-indoleacetic acid

of the enhanced potency is that multiple substitutions alter the electronic configuration of other parts of the molecule in such a way that the molecule can more easily be accommodated by the antigenic receptor site.

Table 3*A* shows the inhibitory effectiveness of other compounds of interest. Epinephrine and norepinephrine inhibit at concentrations of about 100 nmol/1.2 ml; metanephrine and normetanephrine are somewhat more effective. Harmaline is a potent inhibitor compared to yohimbine. The additional ring systems in yohimbine form a bulky group situated where the hapten is thought to bind to the antibody.

Table 3*A* also shows that *N,N*-dimethylated ethylamine (which represents only the side chain of the derivatives) can bind to the antibody at extremely high concentrations, as can *N*-α-dimethylcyclohexanethylamine.

In Table 3*B* are listed the compounds that do not inhibit the antigen–antibody reaction. They include the aromatic amino acids, phenylethyl, and tryptyl derivatives lacking the amino group, and other compounds that may partially resemble the LSD structure, be present in the brain, or have pharmacological activity.

The common structural features possessed by the most effective inhibitors in the phenylethylamine and tryptamine series are an aromatic nucleus and an ethylamine side chain with a dimethylated nitrogen. (One compound containing a propylamine side chain, *N,N*-dimethylhomotryptamine, is an exception to this statement and is discussed in detail above.) Compounds with a free amino group compete much less effectively than the dimethylated derivatives, but much more effectively than compounds lacking the amino group.

Several structural features of the potent inhibitors must be considered in assessing complementarity between hapten and antibody. The methylated N^6 of lysergic acid is rigid, because it is in a ring structure. The pattern of inhibition indicates that in solution the aromatic ring of the phenylethylamine derivatives may be congruous with ring A, and the indole nucleus of the tryptamine derivatives congruous with rings A and B of LSD. The dimethylated nitrogen of phenylethylamine and tryptamine derivatives probably approximates the position N^6 occupies in the LSD molecule. These conformations are in agreement with the chemical considerations and total valence electron calculations of Kang and Green (10) for tryptamine and phenylisopropylamines. Our studies suggest the importance of the *N*-methyl groups (equivalent to the N^6 position of LSD), which apparently orient the side chain correctly and/or contribute to the binding energy between hapten and antibody.

One hypothesis suggests that the *N,N*-dimethyltryptamine derivatives may be endogenous substances causing psychotic episodes resembling the schizoid state (reviewed in refs. 11, 21). These compounds are hallucinogenic, and related compounds have been found in the urine (22). Enzymes that can *N*-methylate indoleamines have been detected in human brain (23).

The pharmacological properties of a compound depend upon many factors other than its interaction with the natural receptor site, e.g., route of administration, absorption, penetration of the blood–brain barrier, rate of metabolism, excretion, and nonspecific adsorption to various macromolecules. Despite these *in vivo* complexities, many studies have shown that LSD and structurally dissimilar compounds produce similar pharmacological effects and show cross tolerance.

We have also observed interactions among these compounds. Of the eight compounds (excluding lysergic acid derivatives) that bind most strongly to the receptor site of the lysergamide antibody (that is, less than about 1 nmol required for 50% inhibition), five are hallucinogenic drugs [5-methoxy-*N*,*N*-dimethyltryptamine, 4-hydroxy-*N*,*N*-dimethyltryptamine, 5-hydroxy-*N*,*N*-dimethyltryptamine, *N*,*N*-dimethyltryptamine, and *N*,*N*-diethyltryptamine (11, 23–27)], one is a sympathomimetic drug [*N*,*N*-dimethyltyramine (28), and one compound, *N*,*N*-dimethylmescaline, was reported to have no pharmacological activity in man or rat (11, 29)]. [Only a few *N*,*N*-dimethylated phenylethylamine- or *N*,*N*-dimethylated phenylisopropylamine-derivatives have been tested for hallucinogenic activity in man (11, 29).] To our knowledge, the pharmacological effects of the eighth compound, *N*,*N*-dimethylhomotryptamine, are unknown.

Many hallucinogenic *N*,*N*-dimethyltryptamine derivatives compete successfully for the receptor site of the antibody to lysergamide. Thus, these compounds *can assume conformations in solution* that resemble part of the LSD structure. Whether these conformations are favored in the absence of antibody or are induced during binding of the compound to the antibody is not known. [Such a receptor site-induced conformational change has been shown; anti-apomyoglobin converts myoglobin to apomyoglobin (30).] The possibility must be considered that these compounds also resemble LSD at physiological receptor sites and that these sites recognize the same structural features in the psychotomimetic compounds that are recognized by the antibody-binding sites. Indeed, differences may exist in the avidity of the physiological receptor sites of different individuals for these compounds (just as antibodies exhibit a range of avidity for a hapten). This could result in selection of the LSD-like conformation and should be considered as a possible mechanism for individual variations in susceptibility to schizophrenia.

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