LSD and Its Lysergamide Cousins

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Lysergic Acid *N,N*-diethylamide (LSD) is the most "famous" (notorious?) of the psychedelics. That dubious distinction came about not only because of its effects, but also because of its extremely high potency. The type of effect it produced was not completely unknown, however, because mescaline had been relatively available to interested persons since the late 1920s, and produced a similar mental state. Aldous Huxley's book *The Doors of Perception* also generated a great deal of interest in mescaline in the 1950s, at least in certain circles, but its low potency (one gram is only 3-4 doses) made it somewhat uneconomical for manufacture. This cost factor may be one of the reasons that it never achieved the popularity gained by LSD in the 1960s and 1970s. By contrast, LSD was easily made from relatively available starting materials such as ergotamine, and its high potency made it economical to manufacture in relatively large quantities. One gram of LSD probably costs no more than a few hundred dollars in raw materials to manufacture, whereas it represents approximately 10,000 clinical doses that could "retail" on the street for upwards of $50,000. Combine this strong economic incentive with the high potency of the drug, which makes distribution easy because doses are very small and easily hidden, and one readily sees some of the factors that led to the high popularity of LSD.

I shall try in this chapter to explain a little bit of the medicinal chemistry of LSD and chemically-related lysergamides so that the reader may gain a better appreciation of the uniqueness of LSD; as the world knows, LSD is no ordinary molecule!

Albert Hofmann has said that LSD resulted from a program of synthesis that involved systematic modification of the lysergamide structure. LSD, actually referred to as LSD-25, was the twenty-fifth compound in a series that he had prepared. When the initial pharmacological screening of LSD-25 in 1938 failed to reveal anything significant, Hofmann says that the compound was shelved, the common practice in a drug company when a compound is found to be uninteresting. Dr. Hofmann notes that a "peculiar presentiment" caused him, some five years later in 1943, to prepare another sample of LSD-25 for further examination, and of course the rest, as they say, is history. This was a very unusual course of events because once the pharmacology department in a drug firm has indicated it has no further interest in a new molecule, it is extremely rare that they can be convinced that they might have missed something, especially based on evidence as flimsy as a "peculiar presentiment." Imagine the head of the pharmacology department in a drug firm being told by a chemist colleague, "Please test this compound again. I just have a feeling that you must have missed something." If the two colleagues are good friends, the job might be done just to humor the chemist, but ordinarily the pharmacologist would simply reply, "Look, we already examined that one and we have many new compounds waiting to be tested for which we have no data at all. We simply don't have time. Sorry."

It is perhaps fortunate that Dr. Hofmann chose to re-examine LSD-25, because in fact we now know that none of the other lysergamides in the series would have been as interesting, nor would they have been potent enough to have provided any effects at all based on the trace amount of compound that Albert Hofmann must have ingested.

Let's now get started by examining the chemical structure of lysergic acid and LSD.

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Lysergic Acid + Diethylamine → Lysergic Acid Diethylamide
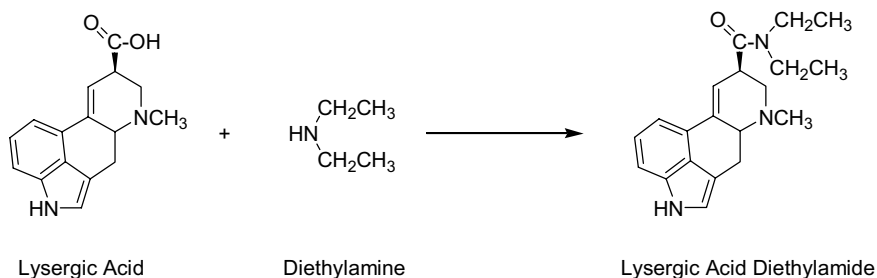
Lysergic acid is typically obtained by treating ergot alkaloids produced by various strains of the "ergot" fungus (e.g. *claviceps purpurea*) with strong alkali such as sodium hydroxide (lye), and then carefully neutralizing the basic mixture with an acid. After suitable purification of the resulting lysergic acid, it is coupled with diethylamine through the use of specific chemical reagents, as shown in the reaction scheme outlined above. In that illustration, note that the OH part at the top of the lysergic acid molecule has been replaced with a nitrogen atom ("N") attached to two CH_2CH_3 units, known as ethyl groups. When amines are chemically linked to acids in this way, the resulting molecules are called amides, and the name diethylamine becomes diethylamide. To simplify awkward chemical names so that they can be discussed in ordinary conversations, chemists often invent shorthand jargon for their molecules. In this case LSD is the acronym for the German name of the compound on the right—lysergic acid diethylamide: **L**yserg-**S**äure-**D**iäthylamid (of course Dr. Hofmann spoke German).

Although ethyl groups have only two carbon atoms (denoted by the letter C in the structures), they are members of a much larger family of carbon atom chains called "alkyl groups." Alkyl groups with only one carbon atom are called methyl groups. Those with three carbon atoms are called propyl groups. Thus, not only do we have diethylamine, but also dimethylamine, dipropylamine, all permutations and combinations of two methyl, ethyl, and propyl groups, as well as a vast array of others with different carbon chain structures. These amines can all be "attached" to lysergic acid to yield lysergic acid dimethylamide, dipropylamide, methylpropylamide, ethylpropylamide, etc., giving many different substitutions on the amide group. Somewhat surprisingly, however, *none* of them approach the potency of LSD, and it is typical that they only have about one-tenth of the activity of LSD. This fact is one of the things we know now that make it so remarkable that Albert Hofmann chose to reexamine only the diethylamide.
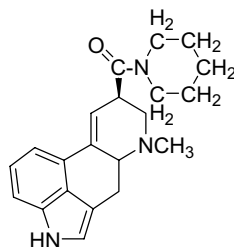
The key to the high activity of LSD lies *specifically in the diethylamide group*. It confers onto LSD both the high potency and the unusual psychoactive properties of the molecule. Indeed, among all the many lysergic acid derivatives that are used for a variety of medicinal purposes, it is the nature of their amide substituent that typically makes them all different. In this chapter we shall try to explore the possible variables that might be involved in conferring this uniqueness. I won't hold you in suspense though, and will state now that the mystery of this fact probably can be attributed to a few specific amino acids contained within the brain serotonin 5-HT_{2A} receptor, and perhaps also within several other brain receptors. Nevertheless, this knowledge does not reveal the secret of exactly how the diethyl groups produce such a specific receptor effect, or why Dr. Hofmann should have had a "presentiment" that ultimately was reflected in the physical properties of a brain receptor that was completely unknown in 1943.

Early Work

For many years after the discovery of LSD, it was thought that it derived its ability to alter human consciousness by blocking the action of the brain neurotransmitter serotonin. That is, LSD could fit into the receptors for serotonin, and prevent it from entering them and having an effect. This idea arose because certain animal tissues, such as the rat uterus, when isolated and placed into a tissue bath, would contract in response to the application of serotonin. Placing LSD into the bath would prevent, or *antagonize*, this contracting action of serotonin. Cerletti and Doepfner (1958) examined a series of lysergamides for this "anti-serotonin activity." Of the five different dialkylamides they studied, LSD was the most potent and specific serotonin antagonist. Activity was reduced either by shortening (i.e. methyl groups) or lengthening (i.e. propyl groups) the amide alkyl chain. The size of the groups also seemed to affect anti-serotonin activity.
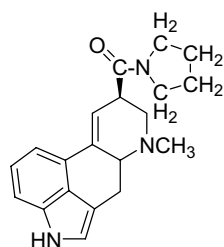
Lysergic Acid Pyrrolidide Lysergic Acid Piperidide Lysergic Acid Morpholide
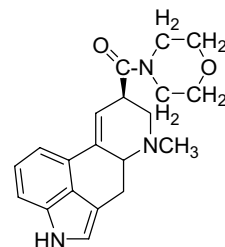
The two ethyl groups were incorporated into ring structures such as the pyrrolidide, piperidide, and morpholide, shown above, but these also had reduced an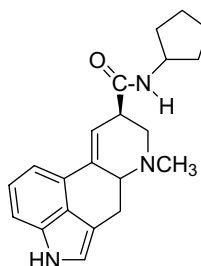ti-serotonin and psychedelic effects (Cerletti and Doepfner 1958). Although the morpholide had less than one-tenth of the potency of LSD in blocking the action of serotonin, it did however have nearly 75% of the potency of LSD as a psychedelic (Gogerty and Dille 1957).

For lysergic acid amides where only one alkyl chain was attached (e.g. lysergic acid monoethylamide), relative antiserotonin activity was related to the length of the alkyl chain. Activity increased with chain length to a maximum of 75% of the potency of LSD with the n-pentylamide (five carbon atoms in a chain) (Cerletti and Doepfner 1958).
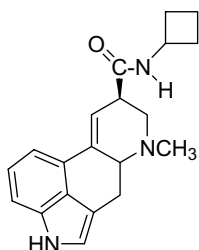
Lysergic Acid Cyclobutylamide Lysergic Acid Cyclopentylamide

Votava et al (1958) prepared a series of cycloalkyl monosubstituted amides in a series from aminocyclopropane (a three-carbon ring system) through aminocycloheptane (a seven-carbon ring system). The aminocyclobutane and aminocylopentane cycloalkylamides, shown above, gave antiserotonin effects in a rat intestine preparation that were 30% *greater* than LSD itself, but the compounds did not have LSD-like effects in man.

Although there are a few other studies from that era where the effect of the amide on biological activity was studied, not much of significance was learned with respect to the reasons for the high potency and uniqueness of the diethyl group.

Studies somewhat later attempted to relate the antiserotonin activity of lysergamides to the degree of lipid solubility of the amide substituent (Dunn and Bederka 1974). Whereas those studies had some measure of success with a limited number of compounds, this property could not account for activity when the amide substituent was part of a cyclic ring.

Clearly, lipid solubility was not the key factor in determining potency for all the different amide substituents that had been studied.

Studies were also carried out in attempts to relate lysergamide activity to the Van der Waals volume of the amide substituents (Gupta et al., 1981), but these were also unsuccessful in explaining the reasons for the unique activity of the diethylamide. Suggestions have been made that the amide substituent might play an indirect role, affecting the overall shape of the molecule, or forcing the carbonyl oxygen group of the amide into a specific orientation.

None of these ideas, however, led to any significant conclusions that could shed light on the reasons that the diethylamide was unique. Indeed, it is not understood, even today, why minor changes in the alkyl groups or using ring systems on the amide lead to loss of activity.

As a general conclusion we can state that nearly any change in the amide group of LSD leads to compounds that have only about one-tenth of the activity of LSD itself, but that we don't know the reasons for this fact.

More Recent Work

Little more was done with lysergamides related to LSD after the late 1950s, except in my laboratory. Even we have so far been puzzled by some of our findings. It is no longer thought, however, that a serotonin blocking action, or *antagonism*, is the effect of LSD in the brain.

Today, the consensus on the mechanism of action of LSD and related tryptamines is that they stimulate, or have an *agonist* effect, at serotonin 5-HT$_2$ receptors (McKenna and Saavedra, 1987; Pierce and Peroutka, 1989; Sadzot et al 1989; Titeler et al 1988; Teitler et al 1990; Branchek et al 1990). This belief largely developed by mechanistic analogy to the hallucinogenic amphetamines (Glennon et al 1983; 1984a; 1984b; 1986), which are nearly full agonists at the 5-HT$_2$ receptor (Sanders-Bush et al 1988) and which do not bind with significant affinity to other known brain sites, except for 5-HT$_{2C}$ receptors.

In addition, further evidence came from the use of 5-HT$_2$-selective antagonists to block the discriminative cue of LSD *in rats* (e.g. Cunningham and Appel, 1987).

More recently, Vollenweider et al. (1998) have shown that the selective 5-HT$_{2A}$ antagonist ketanserin also blocks the effects of psilocybin in humans, providing the most compelling evidence to date that the psychedelics act by stimulating brain 5-HT$_{2A}$ receptors.

The situation is probably not as clear as this, at least with respect to the actions of LSD. Whereas the most important event may be the ability of LSD to interact with brain 5-HT$_{2A}$ receptors, it also has actions at many other brain receptors that may amplify, modulate, or influence its overall effects on consciousness. Indeed, the potency of LSD at the 5-HT$_{2A}$ receptor is not as great as that of some of the amphetamine hallucinogens such as DOB or DOI, yet its human potency is about ten times greater.

In addition, by measures of receptor activation, LSD is only a "partial agonist" (Sanders-Bush et al., 1988). That means that it lacks the ability to activate fully the receptor to the same extent as the natural neurotransmitter serotonin. For example, if we measure the ability of the natural transmitter serotonin to activate the receptor, and define this level of maximum activity as 100%, activation of the receptor by LSD typically only reaches about 20-25% of the maximum.

Clearly, LSD must have some pharmacological property that makes it much more potent than one would expect, based solely on an analysis of its receptor affinity characteristics.

It is not clear what this other effect might be, but LSD is in fact a pharmacologically "dirty" drug, that is rather indiscriminate with respect to the types of receptors to which it binds. The affinity of LSD at many different receptors includes the following:

Table 1. Affinities (in nanomolar) for LSD at various recombinant serotonin receptor subtypes[a]

5HT$_{2A}$ (DOI)[b]	5HT$_{2A}$ (ket)[c]	5HT$_{2C}$ (DOI)	5HT$_{2C}$ (mes)[d]	5HT$_{1A}$	5HT$_{1E}$	5HT$_{5a}$	5HT$_6$	5HT$_7$
3.5	11	5.5	23	1.1	93	7	6	6

[a] Some of these values were obtained through the NIMH-funded receptor screening program

[b] [^{125}I]DOI was used as an agonist radioligand to label the receptor

[c] [^{3}H]ketanserin was used as an antagonist radioligand to label the receptor

[d] [^{3}H]mesulergine was used as an antagonist radioligand to label the receptor

Table 3. A
HT1A recep
two-lever d
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Table 2. Affinities (in nanomolar) for LSD at dopamine, adrenergic, and histamine receptor subtypes.

D_1*	D_2**	D_3	D_4	α_2	H_1
27	6.4	261	230	37	1083

*IC_{50} in rat striatum for D_1;
**IC_{50} in rat striatum for D_2-like.

An examination of the data in Tables 1 and 2 suggests that the most likely candidates for other receptor interactions are probably the 5-HT$_{1A}$ and dopamine D_2 receptors, as well as the 5-HT$_{5a}$, 5-HT$_6$, and 5-HT$_7$ receptors. The importance of the latter three receptors is unknown, but psychedelic tryptamines such as psilocin or *N,N*-dimethyltryptamine do have significant affinity for 5-HT$_{1A}$ receptors. We have recently suggested that this receptor may in fact play an important role in potentiating, or amplifying, the effects of 5-HT$_{2A}$ receptor stimulation (Blair et al., 2000).

There has been previous evidence for functional interactions between 5-HT$_{1A}$ and 5-HT$_2$ receptors. For example, when tested in animal models, 5-HT$_{1A}$ agonists may appear to be 5-HT$_2$ antagonists (e.g. Arnt and Hyttel, 1989). Furthermore, the behavioral syndrome induced in rats by the potent hallucinogen 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) can be stereoselectively blocked by the 5-HT$_{1A}$ antagonists (-)-pindolol or propranolol (Lucki et al, 1984; Tricklebank et al, 1985). Interestingly, an early study by Dixon (1968) had already shown that propranolol could block the disruptive behavior induced by LSD in rats. At the time, this observation was explained as a possible involvement of β-adrenergic receptors in the action of LSD. In 1968 they were not even aware of 5-HT$_{1A}$ receptors; they only knew of the ability of propranolol to block β-adrenergic receptors. In light of present day knowledge, it seems more likely that this effect reflected blockade of the 5-HT$_{1A}$ agonist effects of LSD.

Table 3. Affinity for 5-HT2A and 5-HT1A receptors and potency in the rat two-lever drug discrimination assay for selected lysergic acid amides.

No.	R	R'	Amine Name	Isomer	5-HT$_{2A}$[a]	5-HT$_{1A}$[b]	ED$_{50}$[c]
1	C_2H_5	C_2H_5 (LSD)	diethylamine	N/A	4.8±0.5	4.4±0.77	48 (32-73)
2	H	i-C_3H_7	isopropylamine	N/A	26±0.23	5.2±0.15	110 (86-140)
3	CH_3	i-C_3H_7	methyl isopropylamine	N/A	28±4.5	4.6±0.35	85 (55-130)
4	C_2H_5	i-C_3H_7	ethyl isopropylamine	N/A	17±2.0	3.7±0.48	133 (108-164)
5	i-C_3H_7	i-C_3H_7	diisopropylamine	N/A	17±2.0	18±2.8	351 (250-493)
6	H	$CH(CH_3)C_2H_5$	2-aminobutane	*R*	8.8±0.3	2.0±0.16	33 (17-66)
7	H	"	"	*S*	34±2	4.6±0.33	124 (74-209)
8	H	-$CH(CH_3)C_3H_7$	2-aminopentane	*R*	4.5±0.5	0.6±0.1	102 (61-169)
9	H	"	"	*S*	105±10	8±1	NS
10	H	-$CH(CH_3)C_4H_9$	2-aminohexane	*R*	16±2	0.32±0.0	PS
11	H	"	"	*S*	55±7	4.9±0.3	NS
12	H	-$CH(CH_3)C_5H_{11}$	2-aminoheptane	*R*	80±9	13.9	ND
13	H	"	"	*S*	357±19	35.5	ND
14	H	-$CH(CH_3)C_6H_5$	1-phenethylamine	*R*	20.8±1.2	ND	ND
15	H	"	"	*S*	368±49	ND	ND
16	H	-$CH(C_2H_5)_2$	3-aminopentane	N/A	8.0±0.2	2.1±0.3	52 (24-114)
17	c-C_4H_8	--	Pyrrolidine	N/A	ND	ND	168 (109-258)

[a] K_i in nanomolar for [^{3}H]ketanserin-labeled sites in rat frontal cortex; [b] K_I in nanomolar for [^{3}H]-8-OH-DPAT-labelled sites in rat hippocampus; [c]ED$_{50}$ in nmol/kg for substitution in LSD-trained rats in the two-lever drug discrimination paradigm. ND = not determined. NS = no substitution. PS = partial substitution.
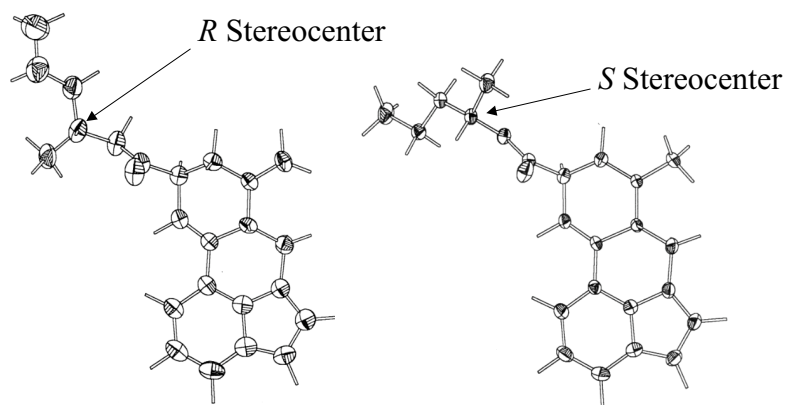
Figure 1. Molecular structures of the lysergamides obtained by x-ray crystallography for amides of lysergic acid with either R- or S-2-aminopentane, on the left and right, respectively (Table 3 entries 8 and 9).

Therefore, in most of our studies we have measured affinity for both the 5-HT$_{2A}$ and the 5-HT$_{1A}$ receptor. In addition, we use a paradigm called two-lever drug discrimination in rats trained to recognize the effects of LSD. This simple animal model has proven over a period of many years to be a useful predictor of LSD-like activity in humans. In Table 3 are presented those data for a number of lysergic acid amides, where we have systematically modified the groups that are attached to the amide function.

In entries 6 - 16, only one alkyl group is attached to the amide. In most of those examples (6 - 15) it was possible to study both optical isomers of the alkyl group, and we observed different effects with the two enantiomers.

Remember that a smaller number means that a compound is more potent. The important thing to note from the table, in the far right column, is the fact that LSD has a potency in rats in the drug discrimination behavioral assay of 48 nanomoles per kilogram of rat body weight. Only two other compounds have comparable activity: entries 6 and 16. Curiously, entry 6 is a monoalkylamide that has the same molecular weight as LSD itself, that is, it has a total of four carbon atoms attached to the amide. Entry 16 has a five-carbon group attached to the amide.

We have no evidence as to whether either of these compounds would be active in man, but these rat data suggest that they might be. The rat behavioral data for entry 3 suggest that it might have about one-half the activity of LSD, and that is close to the observed human activity of about one-third that of LSD.

Column 5 in the table lists the isomer that is more active for monoalkylamides of lysergic acid. Table entries 8 and 9 are lysergamides prepared from the two isomers of 2-aminopentane, where the alkyl group to-

tals five carbons in length.

We were able to obtain crystal structures of these two isomers using x-ray crystallography techniques (Monte et al., 1995). The crystal structures are shown in Figure 1. The chiral carbon atom is indicated by the arrow in each structure. What we note is that the isomers, although they have the same exact molecular weight, have different 3-dimensional structures. Based on the 20-fold higher 5-HT$_{2A}$ receptor affinity of the amide from *R*-2-aminopentane, and if these compounds bind to the receptors in a way that is reflected by their x-ray crystal structures, then we might predict that the receptor can accommodate the long alkyl chain of the amide directed into one region, but not into another.

That is, there is space within the receptor for the five-carbon alkyl group where it is positioned by the *R* isomer, but not where it is placed by the *S* isomer. That is not too surprising, because the receptor is made of L-amino acids, all of which have the same 3-D configuration. Just as a left-handed glove only fits a left hand and a right-handed glove a right one, the 3-dimensional shape within the receptor can properly accommodate only one of these two lysergamide isomers.

Why is it that the *N,N*-diethylamide of LSD is unique? What is it about this function that confers on LSD its particular properties? We have seen that even the most minor modifications of the diethylamide lead to dramatic loss of potency. Even in those cases, we only know that the doses became larger; there is no evidence that if you increase the dosage that the ultimate effect will be the same as that produced by LSD. We would, in fact, predict that the effects should be different because all of the different receptor affinities of a given lysergamide molecule will not shift

in unison and to the same degree when we change the structure of the amide group. These differences are evident even in simple receptor binding assays or rat models.

We have also seen that the receptor is sensitive to changes in stereochemistry, as illustrated in the figure above. These effects *must* be a result of the interaction that occurs between LSD and the 5-HT$_{2A}$ (or any other) receptor with which it interacts. We know that these receptors have a specific structure, that consists of seven alpha-helical proteins bundled together and embedded within the membrane (see also the chapter in this volume by Drs. Charles Nichols and Elaine Sanders-Bush). Furthermore, there is a cavity within these receptors that accommodates and is complementary to the activating drug, in this case LSD. What we are forced to conclude is that the area within the receptor that binds to the diethylamide function of LSD is a specific region that must be just large enough to contain the diethyl groups. If the alkyl groups are not ethyls, they simply don't fit properly. If the two ethyl groups are forced into a cyclic ring, they can't fit either.

Does this make chemical sense? Although it is somewhat unusual that the pharmacology of a drug would be so dependent on the exact size of an attached group, if the group is forced to fit into a constrained region within a receptor or enzyme that is bounded by specific portions of the target molecule, such a phenomenon is not at all surprising. We know from elementary physics principles that two objects of matter cannot occupy the same space at the same time; when the atoms of the ethyl groups bump into unyielding atoms of the receptor, they can push in no further.

We have recently been doing computer-based modeling of the 5-HT$_{2A}$ receptor, based on the 3-dimensional structure of bovine rhodopsin that was published in August 2000 (Palczewski et al., 2000). Rhodopsin has some similarity to brain amine receptors, and current receptor modeling efforts are based on that model. Our preliminary results indicate that the diethylamide group binds within a small cavity that is formed by amino acids located at the top of transmembrane helices 2, 3, 6, and 7. The carbonyl oxygen atom of the diethylamide group appears to form hydrogen bonds to an asparagine residue near the top of transmembrane helix 6 (J. Chambers and D. E. Nichols, unpublished results). The space where the diethylamide binds is bounded on all sides by amino acids that make up the receptor itself. Placing a group larger than a diethylamide into that cavity distorts the receptor, and an alkyl group smaller than a diethyl-amide causes the receptor to change from the shape it adopts when a diethyl group binds, which presumably

is an optimum arrangement.

It will probably be a long time before we understand how subtle changes in the shape of the receptor, or small deformations in its structure, translate into vast differences in activation or inhibition. Translating these receptor effects into actions on consciousness will take a whole lot longer!

I return now to the observation that Dr. Hofmann, in discovering the effects of LSD, had gone back to reexamine the 25th in his original series of lysergamides five years after its original synthesis, because of a "peculiar presentiment." Based on what we know today about the strict limitations on structural change that can be accommodated in the lysergamides, and on the constricted geometry of the receptor domain that binds the diethylamide group of LSD, his desire to focus attention on that one particular and unique compound seems even more baffling!

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