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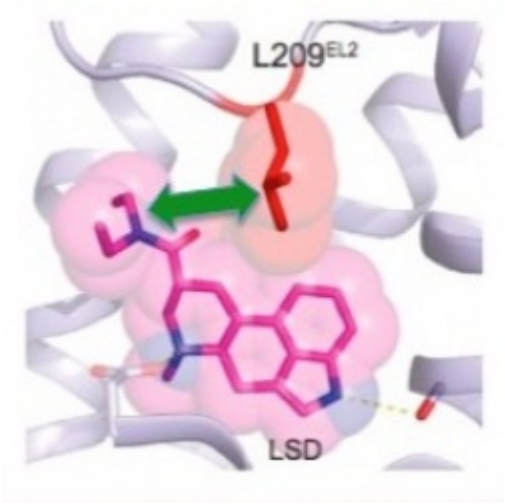
LSD Has Staying Power, Chemistry Explains Why

By Josh Bloom — March 12, 2018



LSD binds to the lid of a serotonin receptor, trapping itself. Image: Cell [1]

LSD is a very interesting drug and not just because of its hallucinogenic properties. It has a reputation of "sticking around" for a fairly long time, even after there is none left in the blood. It likes to stay in the brain. A group from the Department of Pharmacology at the University of North Carolina may have found out why - an unusual mode of binding to a specific receptor in the brain in which the drug traps itself. And it does this because of some rather simple chemistry.

Bryan Roth, M.D, Ph. D., and colleagues recently published a paper [2] in the journal *Cell* entitled *Crystal Structure of an LSD-Bound Human Serotonin Receptor.* The paper contains some very elegant science, in particular, the details of how LSD binds to specific serotonin receptors **(1).** The details of this binding can be visualized at the atomic level by using a technique called x-ray crystallography, a very powerful tool for examining the chemical structures of molecules and how they interact with targets.

But first, let's clean up the name because, although LSD is called "acid," it really shouldn't be, at least according to chemists. Figure 1 explains why this is so.

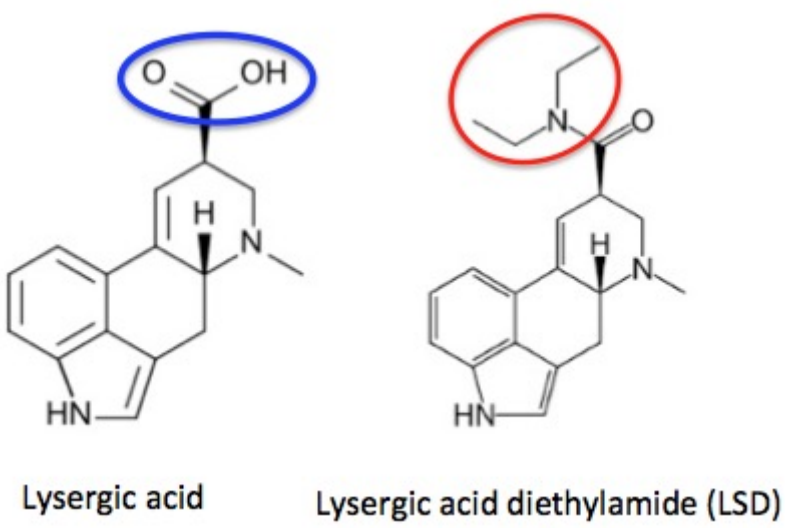


Figure 1. The structures and names of lysergic acid and LSD. The two molecules are identical except for the atoms in the blue and red circles.

Lysergic acid, a natural product which is produced by ergot fungus, has, as the name implies, a functional group called a carboxylic acid (blue circle), hence the name. But lysergic acid is not LSD. LSD is not a natural chemical **(3)**; instead is synthesized in a lab from lysergic acid. The correct name for LSD is **L**y**S**ergic acid **D**iethylamide. But the term "dropping amide" just doesn't sound right, so users took some psychedelic license.

HOW TO VISUALIZE MOLECULES AND RECEPTORS - X-RAY CRYSTALLOGRAPHY

X-ray crystallography **(4)** is a science unto itself. It is highly specialized and technical. An organic chemist *may* be able to understand and use the images that are generated by powerful computers that assemble and process huge amounts of data. But we never really understand the guts of the process, let alone have the knowledge to perform it. This also makes it rather difficult to write about. Here goes nothing.

Roth's group enabled us to see exactly why LSD behaves as it does and it is very cool. The expression "keep a lid on it" is certainly germane here. The image below (Figure 2) shows a simulation of how a very small, but also very critical part of the 5-HT$_{2A}$ serotonin receptor - the target of LSD works **(5)**. The light blue represents a portion of the receptor - the binding site. The dark blue area is an unusual structure called a lid. As the name implies, the lid can either let something out or keep it in. In the closed form (left) nothing is getting in or out of there. In the open form (right) you can see a molecule (red) that is looking rather eager to escape. LSD keeps the lid closed, which is why it stays in your brain longer then you might expect.

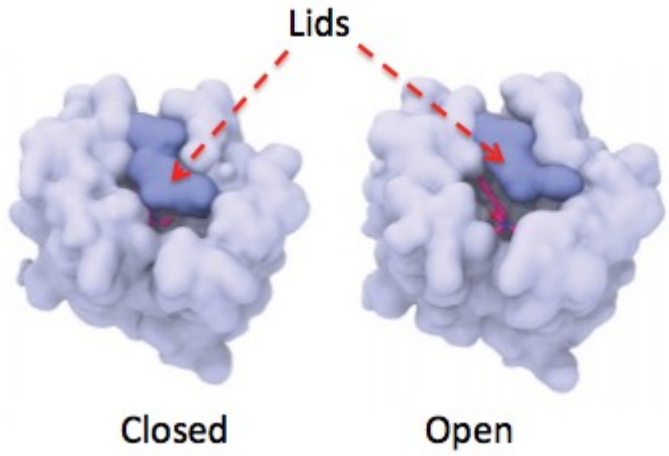


Figure 2. The serotonin receptor that binds LSD. (Left) Closed form. (Right) Open form.

If this isn't cool enough, let's take a closer look, all the way down to the atomic level. Figure 3 shows the precise interaction between the diethylamide portion of LSD and a single amino acid part of the receptor, an amino acid called leucine **(2)**. called leucine. LSD "finds" its serotonin receptor and attaches to its binding site in such a way that the diethylamide from LSD and leucine from the protein are in close proximity. The interplay between the diethylamide part of LSD (pink) and the leucine fragment of the lid protein (red) is shown by the green arrow. They attract each other.

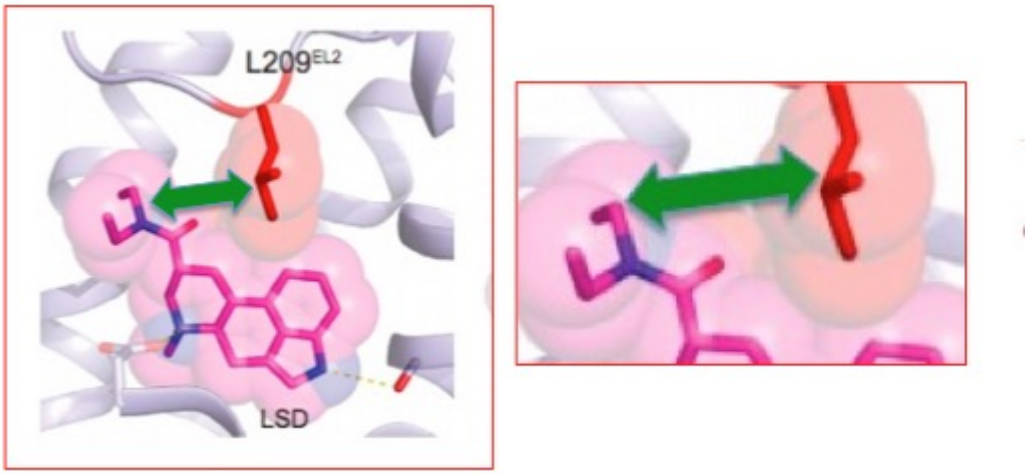


Figure 3. (Left) The interaction (green block arrow) between the diethylamide part of LSD (pink) and a leucine fragment of the receptor (red). (Right) A closeup of the same interaction. L209 refers to the 209th amino acid in the protein chain, which consists of amino acids chemically bound to each other. "L" is shorthand for leucine. Source: Cell [2]

Why should the diethylamide and leucine attract each other? Because of 7th grade chemistry - like attracts like. Figure 4 shows the chemical structure of both fragments and why they "like" each other. Amino acids can be broadly categorized as "hydrophobic" aka lipophilic - hates water but likes oil and "hydrophilic" (likes water but doesn't like oil. When the amino acid contains a group composed only of carbon atoms it is considered to be a hydrophobic amino acid. Leucine (blue circle) is one of these. The four carbon atoms in the diethylamide part of LSD are also hydrophobic. Like attracts like, so these two groups attract each other. It is this attraction that holds the lid closed. Conceptually this is no different than gasoline and water.

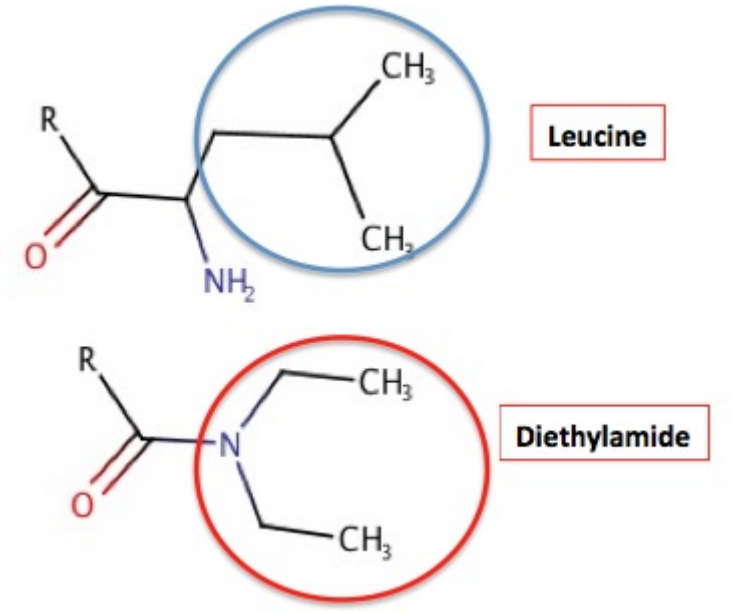


Figure 4. (Top) Leucine contains four hydrophobic carbon atoms - they prefer oil to water. (Bottom) The diethylamide fragment of LSD also contains four hydrophobic carbon atoms. This is why the "stick" together.

It is well known by chemists that the properties of a drug can vary greatly depending only a handful of atoms. It would be difficult to come up with a better example.

NOTES:

(1) There are 14 subtypes [3] of serotonin receptors, found in different locations throughout the body, not just the brain, and they produce a wide array of responses. For example, Zofran, a drug invented to control chemotherapy-induced nausea and vomiting acts by blocking (an antagonist) the type 3 receptor (5-HT3) while Prozac acts as an agonist for the $5HT_{2C}$ receptor.

(2) Proteins are long chains of amino acids chemically bonded together. The properties of the protein depend greatly upon the characteristics of the amino acids. There are 20 different amino acids that make up proteins, and they have very different properties. These different properties are responsible for the enormous number and variety of proteins.

(3) The classification of chemicals as "natural" vs. "synthetic" is a distinction without a difference. As we at ACSH have maintained forever, it makes no difference where a chemical comes from. The structure of the chemical and its properties determine its pharmacological profile, not its origin.

(4) Wikipedia provides [4] a (more or less) understandable description of the process.

(5) 5-HT is short for 5-hydroxytryptamine - another name for serotonin.

Original Paper: Cell, Volume 168, Issue 3 [5], p377–389.e12, 26 January 2017;
https://doi.org/10.1016/j.cell.2016.12.033 [6]

Links
[1] http://www.cell.com/cell/pdf/S0092-8674(16)31749-4.pdf
[2] http://www.cell.com/cell/fulltext/S0092-8674(16)31749-4
[3] https://www.sciencedirect.com/topics/neuroscience/5-ht-receptor
[4] https://en.wikipedia.org/wiki/X-ray_crystallography
[5] http://www.cell.com/cell/issue?pii=S0092-8674(16)X0003-7
[6] https://doi.org/10.1016/j.cell.2016.12.033