XIV. STERIC AND QUANTUM CHEMICAL CHARACTERISTICS:

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The link between the action of psychotomimetic agents and central transmitters seems a promising one. There are probably more transmitters in the brain that have not yet been recognized.

The LSD molecule (Figure 24) is of great interest when one looks at it from the standpoint of trying to determine relationships to chemicals known to be of importance in the brain. LSD can be substituted with various groups (i.e., $-CH_3-$, $-CH_3C\bar{O}-$) at position 1 without loss of activity; at position 2, addition of bromine reduces activity by twenty-fold, and addition of oxygen leads to the normal inactive metabolite. A methoxy group at positions 12 or 13 also abolishes activity.

The double bond between C9 and C10 is essential, and the steric configuration is also vital, d-LSD being active, and L-LSD and both forms of iso-LSD being quite inactive.

Now, in addition to the molecules of 5-HT, nikethamide, and arecoline that people have seen hidden in the molecule LSD, it is also possible to see others. Figure 25 shows how it also contains the molecule of putrescine. The important role of diamines and polyamines in the brain is only just beginning to be realized. As little as 1 nanogram of putrescine in the cat can deplete pituitary follicle-stimulating hormone (FSH), and it is a normal constituent of the median eminence. Addition of a further propylamine group (from S-adenosylmethionine) to putrescine is the normal biosynthetic route for spermidine, which occurs in high concentations in the brain, as well as in other tissues.

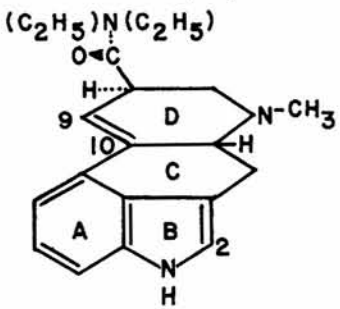

Figure 24. d-LSD.

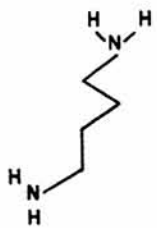

Figure 25. Putrescine arranged in the configuration "hidden" in the molecule of LSD.

Gamma aminobutyric acid (GABA), which is specific to the brain in its hypothetical intramolecular hydrogen bonding, would seem to bear some structural resemblance to barbiturates (Figure 26).

Of all amino acids examined in Snyder's laboratory, only a few localize in synaptosomes after incubation with brain slices. These include glutamic acid, glycine, and serine; glutamic acid and glycine are the most electrophysiologically active amino acids known.

In many cases the so-called "metabolites" of transmitters are not inactive compounds but may themselves have specific, important, physiological roles. For example, imidazole acetic acid, a metabolite of histidine and histamine, has no histamine-like action on the gut but is active on the stretch-receptor in crayfish muscle; similarly, 5-HIAA, methylhistamine, and normetanephrine could all have important functions. If, for example, melatonin had been discovered in the pineal gland, it might have been regarded as an inactive metabolite of serotonin. Some amino acids are, more properly, "membrane active" (Elkes, WS). One should not talk about "excitatory" or "inhibitory" compounds. Polyamines can stabilize membranes and therefore may have important coding functions. Polyamines have also been shown to stabilize both biological membranes and nucleic acids.

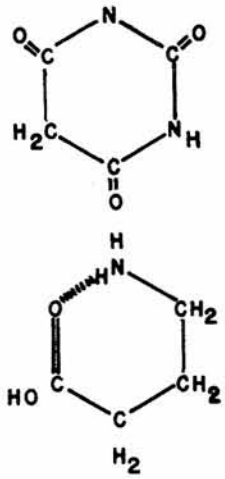

Figure 26. *Upper:* Barbituric Acid. *Lower:* GABA – gamma amino butyric acid (with internal hydrogen bond).

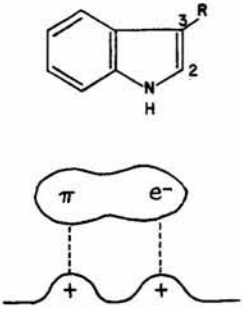

Figure 27. *Upper:* The indolic ring of LSD. *Lower:* Negative charge distribution with potential receptor site diagrammed below it.

Shulgin presented an analysis of the charge-transfer properties of various phenylethylamine molecules. All phenylethylamines can take up the indolic configuration of the B ring of LSD; increasing the number of methoxy groups increases the charge complex by donating electrons on the methoxy groups to the π cloud. The indolic ring, seen side-on, would then appear as shown in Figure 27, with a diffuse negative charge due to this π cloud and a more specific negative charge associated with either the N atom or, more likely, the 3 position. This formation might well interact with positively charged groups on a receptor site, as illustrated.

If a 2-methoxy group was present, ring-forming hydrogen bonding would locate the N too far away from the π cloud to fit onto the postulated receptor site for the indolic nucleus. However, this might be done if the α-C and the N atoms drop below the level of the ring. This molecule could now fit the receptor. The question needs X-ray crystallography to settle it. The geometry of the system would be greatly modified by the methoxy groups, which would change the π cloud (Beveridge, WS). Methoxy groups might also depress activity by preventing complex formation due to steric interference (Green, WS).

Discussion

Smythies pointed out that increasing the number of methoxy groups in the mescaline series (i.e., its 2,3,4,5 and 2,3,4,5,6 analogs) has been shown to increase lipid solubility of the compound also. LSD is some 70 times as lipid soluble as mescaline. The degree of solubility, of course, also determines facility in crossing the blood-brain barrier.

Snyder asked if the NE in the brain acts on α or β receptors. Furthermore, the uptake receptor seems to be different from the postsynaptic receptor. Bradley replied that β blockers are active in the brain but α blockers are not.

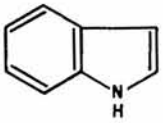

Figure 28. Indole.

Green said that many indoles, and indole itself (Figure 28), can form charge-transfer complexes.

Biologically active indoles like 5-HT may owe part of their activity to this property, but atom-localized properties must determine specificity and potency of the molecules.

Green felt it was important to get away from the idea that the 5-OH group on 5-HT must necessarily have some steric function at the receptor site. It is just as likely that its importance derives from its influence on the electronic characteristics of the whole ring or on the electronic characteristics of other atoms in the ring.

Shulgin pointed out that the quenching of the charge-transfer complex of FMN correlates with hallucinogenic activity and that Paton's dynamics imply that biological activity depends on the rate of action of agonist with receptor rather than on the mere number of receptors filled (Paton, 1961). Elkes suggested that very low energy differences are important at synapses and one therefore has to think in allosteric and charge-transfer terms.

Singer's view of membrane structure (Lenard and Singer, 1966), still purely hypothetical, assumes that the amino acids that have hydrophobic side chains are organized in the alpha helices so that these groups are in close interaction with the nonpolar lipid regions of the membrane (Schmitt, WS).