XIII. STRUCTURE-ACTIVITY RELATIONS:
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Data provided by structure-activity relationship studies can clearly be of importance in elucidating the mode of action of a drug. Smythies presented the complete data available to date for the rat (prepared by his group) and Shulgin presented the human data (Shulgin et al., 1969).

Rat Data

From the rat data the following conclusions can be drawn:

1. The fact that only three methoxylated phenylethylamines are active is probably due to the fact that other potentially active compounds are very rapidly destroyed by amine oxidase in the liver. Pretreatment with MAO before the 4 and 3,4 derivatives greatly increased activity.

2. The 4-methoxy group is sufficient for activity, and Shulgin has confirmed that it has a potency in man of some 6 mescaline units (m.u.). (Dose of n m.u. expresses the fact that a dose of the drug of x/n mg produces a similar effect to x mg of mescaline.)

3. The rat data is complicated by the fact that the animal has only one effective pathway for metabolizing amphetamine, which is by 4-hydroxylation. Thus the 4-methoxy compound produces a long-lasting and irreversible period of disordered behavior, presumably because it cannot be metabolized. In any compound lacking a 4 substitution, however, an hydroxyl group can be inserted at this position leading to an inactive product. Thus the 2,5 compound is active in man, but not in the rat.

4. The pentamethoxy compound is quite active, so the massive accumulation of methoxy groups around the ring does not lead to steric hindrance of its psychotomimetic action, as it does to the action of MAO on the molecule.

5. The N,N-dimethylation of mescaline leads to a marked decrease of activity. The N,N-dimethyl-4-methoxyamphetamine and the N,N-dimethyl derivative of DOM are quite inactive (at 25 mg/kg).

6. No group yet found can substitute for the single sufficient 4-methoxy group. Substitution here by methyl, F, and Cl lead only to compounds with amphetamine-like action.

7. The 2,5-dimethoxy-4-methylamphetamine (DOM) has a complex action. At low doses it acts like an amphetamine, and at higher doses

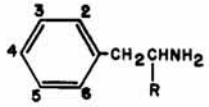
like an hallucinogen. Its human effect is very similar. The 3,4,5-trimethylamphetamine has purely amphetamine properties.

In the tryptamine series a variety of compounds have been tested. N-methyltryptamine was inactive, and 5-methoxy-M,N-dimethyltryptamine was very active. Replacement of the dialkyl groups by a pyridine ring yielded a very active compound.

Human Data

The extensive data now available are presented in Table 4 Shulgin et al., 1969). The only monosubstituted compound tried so far is the 4-methoxy compound, which is hallucinogenic at a potency of some 5 m.u. The 3,4 compound has an undetermined level of activity, but if active, is less potent than mescaline. The most active trimethoxylated material tested was the 2,4,5 – the least, the 2,3,4-trimethoxyamphetamine.

TABLE 4



Substitution pattern						Activity
2	3	4	5	6	R	m.u.
H	H	OCH_3	H	H	CH_3	5
OCH_3	H	OCH_3	H	H	CH_3	5
OCH_3	H	H	OCH_3	H	CH_3	8
H	OCH_3	OCH_3	H	H	CH_3	<1
H	OCH_3	OCH_3	OCH_3	H	CH_3	2.2
OCH_3	H	OCH_3	OCH_3	H	CH_3	17
OCH_3	OCH_3	OCH_3	H	H	CH_3	<2
OCH_3	OCH_3	H	OCH_3	H	CH_3	4
OCH_3	OCH_3	H	H	OCH_3	CH_3	13
OCH_3	H	OCH_3	H	OCH_3	CH_3	10
H	$O-CH_2-O$		H	H	CH_3	3
H	OCH_3	$O-CH_2-O$		H	CH_3	2.7
OCH_3	H	$O-CH_2-O$		H	CH_3	12
OCH_3	$O-CH_2-O$		H	H	CH_3	10
$O-CH_2-O$		OCH_3	H	H	CH_3	3
OCH_3	$O-CH_2-O$		OCH_3	H	CH_3	12
OCH_3	OCH_3	$O-CH_2-O$		H	CH_3	5
OCH_3	OCH_3	OCH_3	OCH_3	H	CH_3	6
OCH_3	H	CH_3	OCH_3	H	CH_3	80

[Shulgin et al., 1969]

Increasing the methoxy groups increases the supply of electrons to the π ring as well as the lipid solubility (and hence access to the brain) and the resistance to MAO. The steric effects will be dealt with in the next section. Orthomethoxylation in general increases activity, and metamethoxylation does not. Substitution of the dimethoxy group by a methylenedioxy group tends to increase activity.

Discussion

Marijuana in large doses has an effect very like LSD. LSD, mescaline, and other drugs of this type cause a rather strange, abrupt cessation of pressing a bar for food. In general, animals have to work hard for food, and with these psychotomimetic drugs they tend not to.

Axelrod asked whether the relative potency of these drugs (within a single species) may not be related to different routes or rates of metabolism as well as to many other functions such as uptake and distribution. Snyder replied by quoting the only data available so far, which is that there is no apparent difference between the metabolism of the highly active 2,4,5 compound and the inactive 2,3,4 compound.

Burns et al. (1967) had reported that 2,5-dimethoxy-β-hydroxyamphetamine (methoxymine) is a potent pressor agent, but no report of any hallucinogenic activity was available. Smythies pointed out that the β-hydroxyl derivative of mescaline is apparently inactive. A question was raised as to how the 2,3,4,5,6 pentamethoxy compound could be active if its "half-molecule" (2,3,4) was inactive. This situation might seem at first sight not to offer any free locus on the ring for nucleophilic attack. Green replied that for such a compound the whole molecule could be regarded as nucleophilic.

Elkes referred to earlier observations (Bradley et al., 1953) in which it was shown that rhythmic photic stimulation enhanced the LSD symptoms in 12 out of 15 normal subjects, and in 3 out of these 12, symptoms were brought out where no symptoms of any kind had been experienced before. An incommunicative trance-like state during photic stimulation following LSD-25 was experienced by 6 subjects; and in 3 there was a slight, transient, but quite definite alteration in muscle tone (not unlike that seen in catatonia), which persisted for up to 20 minutes after photic stimulation had ceased.

Kety wondered if it might be possible to condition an animal to various kinds of hallucination. Ervin identified this as a signal-detection experiment where errors of commission are counted. The animal could be conditioned to the type of geometrical patterns commonly seen in these hallucinoses. Then one could see if the animal responded more with LSD than did a control. This would be getting closer to an animal model of hallucination.

Quarton asked if one could do the experiment in two parts. First, measure performance to show an increase of errors of commission with animals that had never seen the situation before; second, demonstrate that they had been exposed to the situation but show a further increase in number of errors of commission. Kety agreed that this would have to be done in order to demonstrate clearly that there is any relationship to those visual conditioning stimuli.

Efron mentioned some recent experiments on dimethoxyphenylethylamine (DMPEA) in connection with the test that had been developed earlier by Proctor et al. (1968). Proctor and Mahara have now taken the urine of schizophrenics, incubated it with DMPEA, injected it into mice, and then have given the mice amphetamine (private communication). This test showed that they could differentiate between urine from schizophrenics and nonschizophrenics in that the former is lethal to the mice. The experiment was completely blind and has been monitored by qualified observers. The controls were normals, not other patients with mental disorders. However, there were no stressed controls.