Psychopharmacology
of
Hallucinogens

ON THE MOLECULAR MECHANISM OF ACTION OF HALLUCINOGENS

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INTRODUCTION

This paper will describe the application to the problem of the molecular structure of the hallucinogen receptor of a general theory of receptors for neurotransmitters and cognate drugs presented elsewhere (Smythies, 1974; Smythies, 1975). This hypothesis is based on some previous work by Kusnetsov and Ghokov (1962), who suggested that the basis of receptors for transmitters may be two β-pleated chains connected by the opposed complementary amino acids. In a β-pleated chain the amino acids come off alternatively left, right, left, right, etc., and therefore if two such chains are arranged in a parallel array, every other amino acid on each chain can form bonds to each other if they are complementary. In other words, if the amino acid on one chain is arginine and the other is glutamate, these two can form an ionic link; if the amino acid on one chain is glutamine and the other is glutamine, these can form a double hydrogen bonded link; and if the amino acid on one chain is lipophilic such as leucine and the other is also lipophilic, then the two can form a lipophilic interaction. In this way various grids can be built up, to which we have given the name Kusnetsov-Ghokov grids. The exact form of the grids will be determined by the number of rungs in the ladder and the particular amino acids cross-linked. If the amino acids cross-linked are all of much the same length, the two chains will be parallel; but if some are short and some are long, then one will obtain an irregular β-chain.

The most likely link in proteins to be disrupted by a charged transmitter such as acetylcholine would be an ionic link between a positively charged amino acid such as lysine or arginine, and a negatively charged amino acid such as glutamate or aspartate. The strongest link between amino acids possible is the arginine-glutamate double resonating ionic link in view of the extra energy obtained by the resonance involved. In our publications we have pointed out that this structure is not really satisfactory as a model receptor, as the grid is flat and lacks a cup-like character, for which the molecular structure of many drugs which interact at these receptors appear to indicate. The simplest way of converting the flat grid to a receptor cup is to turn each β-pleated chain into a β-pleated sheet by adding a second chain running along the top either anti-parallel or parallel. If this is done extensively, a trench results and this can be converted into a cup either of square or rectangular shape by suitable manipulations as follows: Take, for example, a three-rung ladder of which the lower or primary chains are cross-linked by three arginine-glutamate links. Then, in the secondary chain on top, if the amino acids on rung 1 and 3 are long, and the amino acids over rung 2 are short, a three-dimensional cup is formed, of squarish shape. However, if we start with a 4-rung ladder and inward facing amino acids 1 and 4 of the secondary chains on top are long and the two middle ones are short, then a rectangular shaped cup

is constructed. In fact, however, it is not possible to find any combination of complementary amino acids for the secondary chains in these two end positions which, when cross-linked, are also complementary to an arginine-glutamate pair underneath. This is possible if the amino acids are a glutamine-glutamine pair in the primary chain, because a secondary chain pair glutamine-glutamine is complementary both to the opposite neighbor and to the glutamine-glutamine pair underneath in the primary chain. Furthermore, if we have a methionine-methionine link in the lower primary chains then another methionine-methionine or similar lipophilic link in the upper chains will be complementary and would construct a suitable end wall to the side. But if the pair is arginine-glutamate underneath then there is no possible combination of amino acids which will exert this function. However, we have discovered that the polypeptide chain itself can exert this function if this bends, opposite the insertion of rung 1 into the peptide backbone, through 90° and the peptide chain itself runs along the top of the arginine-glutamate link binding by two hydrogen bonds from the peptide CO and NH. A proline residue at the bend will insure such a right-angle bend.

In these circumstances the other inward-facing amino acids on the secondary chains will determine the molecular binding properties of the site and we have published detailed specifications for different neurotransmitter receptors along these lines. These receptors were designed to fit the known agonists and antagonists at a particular site in such a manner that the receptor is complementary in shape, size and charge and lipophilic distributions to the entire gamut of compounds known to act at the site. Specifications of the three types of acetylcholine receptor have been published (Smythies, 1975) as well as the GABA and glycine receptors (Smythies, 1974), a variety of prostaglandin receptors (Smythies, 1975) and others. These models have been subjected to experimental tests, in particular in our work on convulsants, in which we were able to predict whether convulsants of known chemical structure but of previously unknown physiological mode of action were GABA or glycine antagonists. Our prediction in particular was that tetramethylenedisulfurotetramine (TETS) and cunaniol would be GABA antagonists, which prediction has been verified by experiment (Bowery, Brown and Collins, 1975). We have also predicted a closely allied chemical, cicutoxin, will be a GABA antagonist as well as kopsine. Experimental testing of these predictions is underway.

The present paper describes a similar modeling for the hallucinogen receptor which may or may not be related to the serotonin receptor. In the case of the hallucinogen receptor, we have a number of large and complex molecules which interact with this receptor to give the classical hallucinogenic response. These molecules include d-LSD, dimethyltryptamine, psilocyn mescaline and related compounds.

In our search for a possible complementary molecular structure to these compounds, we started with the largest and most complex, d-LSD. Of this we built a space-filling CPK (Corey-Pauling-Kaltun) model which indicates the following facts. The LSD molecule in the Pauling x-ray structure is composed basically of two flat wedges set at right angles. The larger wedge is composed of the indole ring, B ring and the lower part of the C and D rings. It is very largely composed of the π-cloud character of the indole ring; it also has one positively charged nitrogen at the upper right corner. The second plane of structure is composed of the other part of

the D ring together with the diethylamide side chain. This forms a triangular wedge set at right angles to the larger rectangular shaped wedge underneath. Owing to the profound changes in the effectiveness of LSD, depending on very small changes in this molecular structure, it would seem that this molecule fits very tightly in a complementary receptor which one must assume is made of protein. If we apply our basic hypothesis, these receptors are composed of Kusnetsov-Ghokov grids and we can make the following deductions about the possible nature of the specific receptor for hallucinogens. If we assume that the receptor is made of the basic Kusnetsov-Ghokov grid underneath together with an ancillary secondary chain system on top, the LSD molecule binds with the indole ring "down" and we note that the indole ring is ideally suited to interact with the arg-glu linked bond on each side.

The arg-glu double resonating ionic bond generates two pseudo π-cloud systems, which together are almost as big as the benzene ring due to the guanidine head of the arg and the carboxylic head of the glu on the other side. Two peptide chains cross-linked as described by two arg-glu bonds generate a cavity between the two rungs of the ladder which is complementary in size, shape and molecular properties to the A and B rings of the LSD molecule. It is interesting to note that it is much harder to provide a similar receptor for an indole ring out of what one might normally assume to be complementary amino acids such as tyr, phe or trp itself. This is because of the fact that all these amino acids have only one carbon in between the peptide chain and the ring itself. This means that in almost all positions of the molecule the ring will be situated parallel to the peptide chain and not sticking out at right angles. Thus any grids made of amino acids such as tyr, trp or phe will tend to be much narrower with the two backbones placed closer together than is the case with the arg-glu link in which the constituent amino acids stick out much further from the polypeptide backbone.

In which case a suitable secondary chain arrangement to fit the d-LSD molecule may be constructed as follows: There are only two rungs to the ladder. The sequence of one primary chain (β-sheet) is -glu-x-glu- and of the other is -arg-x-arg- linked by two arg-glu ionic bonds, no. 1 and no. 2. On the glu-x-glu side the peptide chain runs in the direction of (NT to CT) from 2 to 1. The secondary chain on top is anti-parallel and is the F type (Smythies, 1975), as determined by the stereochemical constraints of the system. The sequence required for the secondary chain is -glu-gly-x-gly-pro-x-gly-x. On the arg-x-arg side the primary peptide chain runs from 1 to 2 and the secondary chain is again anti-parallel and of the E type (Smythies, 1975). The sequence required for the secondary chain is -x-gly-pro-x-gly-x- (x residues face outwards and are undetermined). The resultant cavity is trapezoid or wedge shaped in its upper half (Fig. 1) complementary to the wedge shaped D ring plus diethylamide system. The glu can form an ionic bond with the NH^+ of ring D of LSD (Fig. 2). The lower half neatly accommodates the middle ring of LSD between the two pseudo arg-glu π-clouds.

The receptor is also adapted to bind dimethyltryptamine, mescaline and similar compounds but it will not bind any cholinergic, adrenergic or gabergic compounds as these require a four-rung site (Smythies, 1975). On the other hand LSD has activity at other receptors. These all share the primary cross-linked arg-glu primary system with various secondary systems, such that the indole ring of LSD can "intercalate" between the arg-glu

Fig. 1. A CPK model of a theoretical "LSD receptor"

Fig. 2. A CPK model of a molecule of d-LSD (dotted) fitting in its "receptor".

rungs and the triangular wedge of the D ring plus diethylamide system can occupy part of the receptor cavity, although the "fit" is much less precise.

This hypothesis of the structure of the receptor may be experimentally tested by designing possible agonists and antagonists at the site by means of CPK molecular models and then testing them in the standard pharmacological systems for hallucinogens and their blockers.

CPK molecular models of these molecular arrangements were demonstrated at the meeting.

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Fitting