Psychopharmacology of Hallucinogens

MOLECULAR DETERMINANTS FOR INTERACTION WITH THE LSD RECEPTOR: BIOLOGICAL STUDIES AND QUANTUM CHEMICAL ANALYSIS

Jack Peter Green, Carl Lynn Johnson, Harel Weinstein, Sungzong Kang and David Chou

Department of Pharmacology, Mount Sinai School of Medicine, Of the City University of New York, New York, New York 10029

5-Hydroxytryptamine (5-HT) is widely distributed and potently active on many tissues in some of which it appears to react with sites similar to those of D-lysergic acid diethylamide (D-LSD) and some other hallucinogenic compounds. For these reasons, a search for the molecular structural characteristics that determine the effects of these and related substances has attracted attention (Johnson et al. 1975; Green et al. 1974). About ten years ago, efforts began to use quantum mechanics to learn the electronic characteristics of specific atoms in the indole ring that could account for the activities of 5-HT and other tryptamines (Merril et al., 1966; Green, 1966, 1967). This work was given impetus with the availability of more sophisticated quantum mechanical methods. These were used to account quantitatively for the potencies of tryptamines on the D-LSD receptor in the fundus of the stomach (Green and Kang, 1970).

We describe here the results of studies on the potencies of tryptamines on three different biological systems and the molecular electronic correlates of the potencies. The biological measurements are: contraction of the fundus of the rat stomach; inhibition of high affinity binding of D-LSD to rat brain membranes; and inhibition of uptake of 5-HT by rat synaptosomes. Only the last lacks sensitivity to D-LSD.

As well as doing total valence electron calculations, we studied the molecular reactivity of some of the tryptamines by new theoretical methods (Weinstein et al. 1974; Bartlett and Weinstein, 1975; Politzer and Weinstein, 1975; Chang et al. 1976) using ab-initio calculations.

Biological Studies

Activities of Tryptamines on the Isolated Stomach of the Rat

5-HT in low concentrations (10^{-10} to 10^{-6} M), like many other tryptamines, contracts the isolated fundus of the stomach of the rat, an effect that is blocked by brom-LSD i.e. 2-bromolysergic acid diethylamide (BOL) and D-LSD (Vane, 1957; Barlow and Khan, 1959a,b; Offermeier and Ariens, 1966 a,b; Winter et al. 1967; Pinder et al. 1971; Barzaghi et al. 1973). Mescaline, amphetamine and some other phenylalkylamines also contract the fundal strip

and their effect too is blocked by brom-LSD as well as other 5-HT antagonists, e.g., mianserin and methylsergide (Vane, 1957, 1960; Innes, 1963; Innes and Kohli, 1969; Frankhuijzen and Bonta, 1974a). The 5-HT receptor in this tissue is very similar or even identical to the α-adrenergic receptor. α-Adrenergic blocking agents antagonize both 5-HT and amphetamine in this preparation (Vane, 1957; Innes, 1963; Frankhuijzen and Bonta, 1974b; Frankhuijzen, 1975). Both amines protect the receptor against α-adrenergic blockade (Innes, 1963). And the α-adrenergic blockers compete with mianserin and methylsergide for the same receptor (Frankhuijzen and Bonta, 1974a,b).

In an effort to define the molecular requirements for activation of this receptor, we first looked for a correlation between the electronic structure of the tryptamines (Kang and Green, 1969) and their potency as measured by Vane (1959). Among five tryptamines bearing different substituents at the 5 position of the ring, potency correlated almost precisely with decreasing resonance constants. This suggested that high electron density at the active site or sites of the molecule is associated with activity (Kang and Green, 1969). This finding clearly revealed that the substituents on the ring altered biological activity because of an effect they had on the electronic density in the ring system. The use of resonance constants for a correlation cannot indicate which atom(s) is involved in the activity. To identify the specific sites, we then carried out molecular orbital calculations on the nine ring-substituted tryptamines tested by Vane (1959). Potency was found to be correlated with specific electronic characteristics on three different atoms in the ring (Green and Kang, 1970).

This study has now been extended with another method of molecular orbital calculation which is suitable for handling molecules having a chlorine substituent. In addition, this analysis prompted the study of the action of twelve additional tryptamine derivatives on the fundus. We sought correlations between potency and molecular structure, using the results of theoretical (quantum chemical) analysis.

Methods. Potency of the tryptamines was measured by the method of Vane (1957). A strip of longitudinal muscle (approximately 2 mm wide and 2 cm long when stretched) was placed in a 10 ml muscle bath at 37°C. The buffer was Krebs-Henseleit, supplemented with 10^{-7} M scopolamine hydrobromide and 10^{-5} M iproniazid phosphate, bubbled continuously with 95% O_2-5% CO_2. Drugs were added in a volume of 0.1 ml or less from a microliter syringe. Contractions were recorded on a Clevite Brush Mark 220 recorder with a Grass Force-Displacement Transducer FT03C. The potencies were obtained by estimating the concentrations of the tryptamine derivative and 5-HT that give the same contraction of the rat fundus: dose-response curves for the tryptamine analogs were always compared to the dose-response curve of 5-HT run on the same tissue since the concentration of 5-HT giving 50 percent of maximal contraction varied markedly in different fundus strips. Only those experiments in which the dose-response curves of the tryptamine analogs were parallel to that of 5-HT were used. In these circumstances parallel lines were fit to the data by eye and the equipotent molar ratios (MR) calculated as the ratio of the molar concentration of the tryptamine derivative to the molar contraction of 5-HT required to produce the same contraction. Occasionally, a tryptamine derivative, which in all previous experiments had yielded dose-response curves paralleling the 5-HT curve, failed to give a parallel response, and this experiment was discarded. However, as described below, certain derivatives consistently gave non-parallel curves.

Non-parallel dose-response curves strongly suggest that the agonists are not acting in the same way e.g., that they are acting on more than one receptor. Any compound that did not give a dose-response curve parallel to that of 5-HT was not entered into the regression analysis. Those tryptamines that did not give parallel dose-response curves were the 6,7-$(OH)_2$, 5-benzyloxy, 7-benzyloxy, and 7-OH derivatives. Another indication that a series of agonists acts on the same or similar receptor may be obtained by doing dose-response curves before and after blockade with an irreversible antagonist (Furchgott, 1966). Correlation of the potencies with the affinity constants provides further evidence that only one receptor is involved in the action of the compounds.

The affinity constants, i.e., the reciprocal of the agonist dissociation constants, were measured with the use of an irreversible antagonist, phenoxybenzamine, by a method described by Furchgott (1966). Complete dose-response curves to a tryptamine derivative were obtained before and after exposure of the fundus strip to phenoxybenzamine, 2.5×10^{-6} M, for 10 min. A computerized curve fitting procedure was used to calculate the agonist affinity constant (Parker and Waud, 1971). At least three different fundus strips were used for each tryptamine derivative, and the molar ratios were measured on strips different from those used to measure the affinity constants.

All tryptamine derivatives, with the exception of 5-fluorotryptamine (K and K Laboratories) and tryptamine (Sigma), were synthesized by Regis Chemical Co. (Morton Grove, Ill.) and obtained through Dr. Albert Manian of the National Institute of Mental Health (Manian, 1974). Iproniazid phosphate was obtained from Sigma, scopolamine hydrobomide from K and K Laboratories, D-LSD-25 from Sandoz through Ms. Jacqueline Bryant of the National Institute on Drug Abuse, and phenoxybenzamine from Smith, Kline and French. We are grateful for these gifts.

Results. Table 1 shows the original results of Vane (1959) (column A), our original results in the absence of ascorbic acid (column B of Table 1) and our results in the presence of ascorbic acid (column C of Table 1). All values are calculated relative to 5-HT in the absence of ascorbic acid (column B). The relative activities of the analogues of tryptamine are expressed in terms of molar potencies equiactive with 5-HT(=1).

In our initial studies on the fundus, the tryptamine derivatives were freshly dissolved in water and stored on ice for each day's experiment. The molar ratios obtained by us under these conditions are shown in column B of Table 1. Our values for tryptamine and 5-methoxytryptamine agree reasonably well with the 1959 study of Vane (column A of Table 1). However, during the course of these experiments we noted that several of the tryptamines yielded slightly colored solutions when dissolved in water (especially the 5,7-$(OH)_2$ and 5,6-$(OH)_2$ derivatives). This pigment formation was considerably reduced by dissolving the tryptamines in 10 mM ascorbic acid. Under these conditions several of the tryptamines were more potent, i.e. they had significantly lower molar ratios (column C of Table 1). Surprisingly, this was true even for tryptamine and the 5-F derivative, compounds that are considered relatively stable. The 4-NH_2 derivative formed a blue pigment when dissolved in water at room temperature. Ascorbic acid did not greatly affect the stability. Pigment formation could be prevented by dissolving the compound in cold water, when it was immediately tested. However, after storage in the frozen state overnight a blue pigment was apparent and activity on two fundus strips had decreased to 25 per cent of the activity of the fresh

SUMMARY

1. Potencies of a series of tryptamines were measured in three different systems: contraction of the fundus of the rat stomach; inhibition of binding of D-LSD by rat brain membranes; inhibition of uptake of 5-HT by crude rat synaptosomes.
2. The potencies in contracting the stomach correlated (r=0.94) with potencies in inhibiting D-LSD binding by brain membranes.
3. The potencies correlated with frontier electron densities on the indole ring: N1, C3, C4, and C5.
4. These positions correspond to the sites at which the density of the highest occupied molecular orbital is localized on 5-HT.
5. Results from ab-initio molecular orbital calculations were used to define reactivity indices for tryptamines: electrostatic interaction potentials and maps of susceptibility to polarization.
6. These indices showed the importance of C4-C5 and the bridge (i.e., C8-C9) regions in polarization complexes such as postulated for interaction with the receptor.
7. From the electrostatic potential maps, force vectors were derived indicating the preferred orientation of the indole ring with another molecule such as a receptor.
8. The vector of the most potent compound, 5-HT, was shown to be perpendicular to that of the least potent compound, 6-HT. The biological consequences of this difference in orientation are discussed.
9. The reactivity indices were tested by calculating the interaction of tryptamines with positive species (e.g., a proton) at various atoms in the indole ring.
10. The resulting interaction energies support the validity of using electrostatic interaction potentials as reactivity indices.
11. The indole nitrogen and carbon atoms respond to the interaction with a proton in a markedly different way. Carbon atoms accumulate the charge, the nitrogen atom transfers it to its neighboring atoms. This charge transduction by nitrogen activates the neighboring atoms for polarization interaction.
12. The interaction of 5-HT as an electron donor with imidazolium as an electron acceptor was studied (in different geometries) as a model of the interaction of tryptamines with receptor sites.
13. The results supported the use of force vectors as criteria for the orientation of reacting molecules in polarization complexes.
14. The charge redistribution resulting from the 5-HT interaction with imidazolium showed that charge transduction occurs when a positive site on imidazolium interacts with the indole nitrogen. This transduction strengthens the complex and could help to explain the importance of nitrogen in activity.

Acknowledgments

This work was supported by a grant from the National Institute of Mental Health (MH-17489). We are grateful to Dr. Albert A. Manian of the National Institute of Mental Health for providing most of the tryptamines; to Ms. Jacqueline Bryant of the National Institute on Drug Abuse for the LSD; Dr. W.F. Raub and the Chemical/Biological Information Handling Program, Division of Research Resources, National Institutes of Health, for providing access to the PROPHET System which is a specialized computer resource developed especially for studying the relationship between chemical structure and biological activity; a detailed description of PROPHET and its application appears in the Proceedings of the National Computer Conference and Exposition, May 6-10, 1974, Chicago.

REFERENCES

Baker, R.W., Chothia, C., Pauling, P. and Weber, H.P., Molecular structures of hallucinogenic substances: lysergic acid diethylamide, psilocybin, and 2,4,5-trimethoxy-amphetamine, Mol. Pharmacol. 9, 23 (1973).

Barlow, R.B. and Kahn, I., Actions of some analogues of tryptamine on the isolated rat uterus and on the isolated rat fundus strip preparations, Brit. J. Pharmacol. 14, 99 (1959a).

Barlow, R.B. and Kahn, I., Actions of some analogues of 5-hydroxytryptamine on the isolated rat uterus and the rat fundus strip preparations, Brit. J. Pharmacol. 14, 265 (1959b).

Bartlett, R.J. and Weinstein, H., Theoretical treatment of multiple site reactivity in large molecules, Chem. Phys. Lett. 30, 441 (1975).

Barzaghi, F., Baumgartner, H.R., Carruba, M., Mantegazza, P. and Pletscher, A., The 5-hydroxytryptamine-like actions of 5,6-dihydroxytryptamine, Brit. J. Pharmacol. 48, 245 (1973).

Bennett, J.L. and Aghajanian, G.K., D-LSD binding to brain homogenates: possible relationship to serotonin receptors, Life Sci. 15, 1935 (1975).

Bennett, J.P., Jr. and Snyder, S.H., Serotonin and lysergic acid diethylamide binding in rat brain membranes: relationship to postsynaptic serotonin receptors, Mol. Pharmacol. 12, 373 (1976).

Bennett, J.P., Jr. and Snyder, S.H., Stereospecific binding of D-lysergic acid diethylamide (LSD) to brain membranes: relationship to serotonin receptors, Brain Res. 94, 523 (1975).

Bergmann, E.D. and Pullman, B (Ed.), Molecular and Quantum Pharmacology, Reidel, Boston (1974).

Burt, D.R., Creese, I. and Snyder, S.H., Binding interactions of lysergic acid diethylamide and related agents with dopamine receptors in the brain, Mol. Pharmacol. 12, 631 (1976).

Castleman, P.A., Russell, C.H., Webb, F.N., Hollister, C.A., Siegel, J.R., Zdonik, S.R. and Fram, D.M., AFIPS Conference Proceedings 43, 457 (1974).

Chang, S-Y, Weinstein, H. and Chou, D., Perturbation treatment of multiple site reactivity: molecule-molecule interactions, Chem. Phys. Lett. 42, 145 (1976).

Chou, D. and Weinstein, H., Reactive site induction by proton attack in heterocyclic rings, 7th ACS Regional Meeting, Albany, New York, (1976).

Clementi, E., Study of the electronic structure of molecules. VI. Charge-transfer mechanism for the $NH_3+HCl \rightleftharpoons NH_4Cl$ reaction, J. Chem. Phys. 47, 2323 (1967).

Creese, I., Burt, D.R. and Snyder, S.H., The dopamine receptor: differential binding of d-LSD and related agents to agonist and antagonist states, Life Sci. 17, 1715 (1976).

Daly, J.W. and Witkop, B., Selective exchange of nuclear protons in hydroxy-indoles, J. Amer. Chem. Soc. 89, 1032 (1967).

Farrow, J.T. and Van Vunakis, H., Characteristics of d-lysergic acid diethylamide binding to subcellular fractions derived from rat brain, Biochem. Pharmacol. 22, 1103 (1973).

Fillion, G., Fillion, M-P., Spirakis, C., Bahers, J-M. and Jacob, J., Life Sci. 18, 65 (1976).

Foster, R. and Fyfe, C.A., Electron-donor-acceptor complex formation by compounds of biological interest. Part III. Indole Complexes, J. Chem. Soc. (B) 926 (1966).

Frankhuijzen, A.L., Analysis of ergotamine-5-HT interaction on the isolated rat stomach preparation, Eur. J. Pharmacol. 30, 205 (1975).

Frankhuyzen, A.L. and Bonta, I.L., Effect of mianserin, a potent anti-serotonin agent, on the isolated rat stomach fundus preparation, Eur. J. Pharmacol. 25, 40 (1974a).

Frankhuijzen, A.L. and Bonta, I.L., Receptors involved in the action of 5-HT and tryptamine on the isolated rat stomach fundus preparation, Eur. J. Pharmacol. 26, 220 (1974b).

Furchgott, R.F., The use of beta-haloalkylamines in the differentiation of receptors and the determination of dissociation constants of receptor agonist complexes, Advan. Drug Res. 3, 21 (1966).

Green, J.P., Synthesis, uptake and binding of histamine and 5-hydroxytryptamine in mast cells, in Euler, U.S. von, Rosell, S., and Uvnas, B. (ed.), Mechanisms of Release of Biogenic Amines, p. 12, Pergamon, New York, 1966.

Green, J.P., The application of quantum mechanics to pharmacology: some substances active in the nervous system, in Walaas, O. (ed), Molecular Basis of Some Aspects of Mental Activity, vol. 2, p. 95, Academic, New York, 1967.

Green, J.P. and Kang, S., The correlation of electronic structures of indole derivatives with their biological activities, in Kier, L.B. (ed.), Molecular Orbital Studies in Chemical Pharmacology, p. 105, Springer, New York, 1970.

Green, J.P. and Malrieu, J.P., Quantum chemical studies of charge-transfer complexes of indoles, Proc. Nat. Acad. Sci., U.S.A. 54, 659 (1965).

Green, J.P., Kang, S. and Margolis, S., Molecular characteristics of histamine and 5-hydroxytryptamine pertinent to binding, Memoirs Soc. Endocrinol. 19, 727 (1971).

Green, J.P., Dressler, K.P. and Khazan, N., Mescaline-like activity of 2-amino-7-hydroxytetralin, Life Sci. 12, 475 (1973).

Green, J.P., Johnson, C.L. and Kang, S., Application of quantum chemistry to drugs and their interactions, Ann. Rev. Pharmacol. 14, 319 (1974).

Handschumacher, R.E. and Vane, J.R., The relationship between the penetration of tryptamine and 5-hydroxytryptamine into smooth muscle and the associated contractions, Brit. J. Pharmacol. 29, 105 (1967).

Hansch, C., Structure-Activity Relationships, Intern. Encyclopedia Pharmacol. Therap., Vol. 1, Cavallito, ed., Pergamon Press, New York, 1973.

Heikkila, R.E. and Cohen, G., The inhibition of (^{3}H) biogenic amine accumulation into rat brain tissue slices by various tryptamine derivatives, Res. Commun. Chem. Pathol. Pharmacol. 7, 539 (1974).

Hélène, C., Dimicoli, J-L. and Brun, F., Binding of tryptamine and 5-hydroxytryptamine (serotonin) to nucleic acids. Fluorescence and proton magnetic resonance studies, Biochem. 10, 3802 (1971).

Horn, A.S., Structure-activity relations for the inhibition of 5-HT uptake into rat hypothalamic homogenates by serotonin and tryptamine analogues, J. Neurochem. 21, 883 (1973).

Horn, A.S., Baumgarten, H.G. and Schlossberger, H.G., Inhibition of the uptake of 5-hydroxytryptamine, noradrenaline and dopamine into rat brain homogenates by various hydroxylated tryptamines, J. Neurochem. 21, 233 (1973).

Horn, A.S., Post, M.L., Kennard, O. and DiSanseverino, L.R., A crystallographic and theoretical study of the conformation of DOET and its significance for the hallucinogenic amphetamines, J. Pharm. Pharmacol. 27, 13 (1975).

Innes, I.R., Action of dexamphetamine on 5-hydroxytryptamine receptors, Brit. J. Pharmacol. 21, 427 (1963).

Innes, I.R. and Kohli, J.D., Excitatory action of sympathomimetic amines on 5-hydroxytryptamine receptors of gut, Brit. J. Pharmacol. 35, 383 (1969).
Johnson, C.L., Applications of the PROPHET system in molecular pharmacology structure-activity relationships in monoamine oxidase inhibitors, AFIBS Conference Proceedings 43, 473 (1974).
Johnson, C.L. and Green, J.P., Molecular orbital studies on tryptamines active on the LSD receptor of the rat fundus strip, Int. J. Quantum Chem. QBS 1, 159 (1974).
Johnson, C.L., Kang, S. and Green, J.P., Conformational analysis by a combined molecular-orbital-classical procedure, in Bergmann, E.D. and Pullman, B. (ed), Conformation of Biological Molecules and Polymers, p. 517, Israel Acad. Sci., Jerusalem, 1973.
Johnson, C.L., Kang, S. and Green, J.P., Stereoelectronic characteristics of LSD and related hallucinogens, in Sankar, D.V.S. (ed.), LSD-A Total Study, p. 197, PJD, Westbury, 1975.
Kang, S. and Cho, M-H., Conformational analysis of 5-hydroxytryptamine and its cation: ψ, ϕ-energy contour diagram by the INDO molecular orbital method, Theoret. chim. Acta 22, 176 (1971).
Kang, S. and Green, J.P., Resonance constants and the activities of indolealkylamines on stomach muscle, Nature 222, 794 (1969).
Kang, S. and Green, J.P., Steric and electronic relationships among some hallucinogenic compounds, Proc. Nat. Acad. Sci. U.S.A. 67, 62 (1970).
Kang, S., Johnson, C.L. and Green, J.P., The conformation of 5-hydroxytryptamine, J. Mol. Struct. 15, 453 (1973a).
Kang, S., Johnson, C.L. and Green, J.P., Theoretical studies on the conformations of psilocin and mescaline, Mol. Pharmacol. 9, 640 (1973b).
Klyne, W. and Prelog, V., Description of steric relationships across single bonds, Experientia 16, 521 (1960).
Knapp, S. and Mandell, A.J., Coincidence of blockade of synaptosomal 5-hydroxytryptamine uptake and decrease in tryptophan hydroxylase activity: effects of fenfluramine, J. Pharmacol. Exp. Therap. 198, 123 (1976).
Kuhar, M.J., Aghajanian, G.K. and Roth, F.H., Tryptophan hydroxylase activity and synaptosomal uptake of serotonin in discrete brain regions after midbrain raphe lesions: correlations with serotonin levels and histochemical fluorescence, Brain Res. 44, 165 (1972).
Leo, A., Hansch, C. and Elkins, D., Partition coefficients and their uses, Chem. Rev. 71, 525 (1971).
Lovell, R.A. and Freedman, D.X., Stereospecific receptor sites for d-lysergic acid diethylamide in rat brain: effects of neurotransmitters, amine antagonists, and other psychotropic drugs, Mol. Pharmacol. 12, 620 (1976).
Lowry, O.H., Rosebrough, N.J., Farr, A.L., Randall, R.J., Protein measurement with the folin phenol reagent, J. Biol. Chem. 193, 265 (1951).
Manian, A.A., NIMH-sponsored chemical synthesis program, Psychopharmacol. Bull. 10, 51 (1974).
Menon, M.K., Tseng, L-F. and Loh, H.H., Pharmacological evidence for the central serotonergic effects of monomethoxyamphetamines, J. Pharmacol. Exper. Therap. 197, 272 (1975).
Merril, C.R., Snyder, S.H. and Bradley, D.F., Inhibition of histamine methyltransferase by serotonin and chlorpromazine derivatives: electronic aspects, Biochim. Biophys. Acta 118, 316 (1966).
Millié, P., Malrieu, J.P., Benaim, J., Lallemand, J.Y. and Julia, M., Researches in the indole series. XX. Quantum mechanical calculations and charge-transfer complexes of substituted indoles, J. Med. Chem. 11, 207 (1968).

Nogrady, T., Hrdina, P.D. and Ling, G.M., Investigation into the association between serotonin and adenosine triphosphate in vitro by nuclear magnetic resonance and ultraviolet spectroscopy, Mol. Pharmacol. 8, 565 (1972).

Offermeier, J. and Ariëns, E.J., Serotonin. I. Receptors involved in its action, Arch. int. Pharmacodyn. 164, 192 (1966a).

Offermeier, J. and Ariëns, E.J., Serotonin. II. Structural variation and action, Arch. int. Pharmacodyn. 164, 216 (1966b).

Parker, R.B. and Waud, D.R., Pharmacological estimation of drug-receptor dissociation constants. Statistical evaluation. I. Agonists, J. Pharmacol. Exp. Therap. 177, 1 (1971).

Pert, C.B. and Snyder, S.H., Properties of opiate-receptor binding in rat brain, Proc. Nat. Acad. Sci. U.S.A. 70, 2243 (1973).

Pinder, R.M., Green, D.M. and Thompson, P.B.J., Comparative pharmacology of 5-hydroxytryptamine and its benzofuran, benzo[b]thiophen, and indene isosteres, J. Med. Chem. 14, 626 (1971).

Politzer, P. and Weinstein, H., Molecular electrostatic potentials-II mechanistic aspects of electrophilic interactions of some five-membered heterocycles, Tetrahedron 31, 915 (1975).

Pople, J.A. and Segal, G.A., Approximate self-consistent molecular orbital theory. III. CNDO results for AB_2 and AB_3 systems, J. Chem. Phys. 44, 3289 (1966).

Pullman, A., SCF ab initio study of the protonation of the peptide bond, Chem. Phys. Lett. 20, 29 (1973).

Raub, W.F., The PROPHET system and resource sharing, Fed. Proc. 33, 2390 (1974).

Sapper, H. and Lohmann, W., Self-association and binding sites of some psychotomimetic tryptamine derivatives and related compounds: nuclear magnetic resonance investigations, Mol. Pharmacol. 12, 605 (1976).

Shinitzky, M. and Katschalski, E., Complexes between indole and imidazole derivatives of the charge-transfer type, in Pullman, B. (ed.) Molecular Associations in Biology, p. 361, Academic, New York, 1968.

Shinitzky, M., Katchalski, E., Grisaro, V. and Sharon, N., Inhibition of lysozyme by imidazole and indole derivatives, Arch. Biochem. Biophys. 116, 332 (1966).

Shulgin, A.T., Sargent, T. and Naranjo, C., Structure-activity relationships of one-ring psychotomimetics, Nature 221, 537 (1969).

Snyder, S.H. and Bennett, J.P., Jr., Biochemical identification of the post-synaptic serotonin receptor in mammalian brain, in Usdin, E. and Bunney, W.E. Jr. (ed.) Pre- and Postsynaptic Receptors, p. 191, Dekker, New York, 1975.

Sonneville, P.F., An indirect action of dopamine on the rat fundus strip mediated by 5-hydroxytryptamine, Eur. J. Pharmacol. 2, 367 (1968).

Tessel, R.E. and Rutledge, C.O., Specificity of release of biogenic amines from isolated rat brain tissue as a function of the meta substituent of N-ethylamphetamine derivatives, J. Pharmacol. Exper. Therap. 197, 253 (1976).

Thewalt, U. and Bugg, C.E., The crystal and molecular structure of serotonin picrate monohydrate, Acta Cryst. B28, 82 (1972).

Truhlar, D.G., Van-Catledge, F.A. and Dunning, T.H., Ab initio and semi-empirical calculations of the static potential for electron scattering off the nitrogen molecule, J. Chem. Phys. 57, 4788 (1972).

Tseng, L-F., Menon, M.K. and Loh, H.H., Comparative actions of monomethoxy-amphetamines on the release and uptake of biogenic amines in brain tissue, J. Pharmacol. Exp. Therap. 197, 263 (1976).

Tute, M.S., Principles and practice of Hansch Analysis: a guide to structure-activity correlation for the medicinal chemist, Adv. Drug Res. 6, 1 (1971).

Ungar, F., Hitri, A. and Alivisatos, S.G.A., Drug antagonism and reversibility of the binding of indoleamines in brain, Eur. J. Pharmacol. 36, 115 (1976).

Vane, J.R., A sensitive method for the assay of 5-hydroxytryptamine, Brit. J. Pharmacol. 12, 344 (1957).

Vane, J.R., The relative activities of some tryptamine analogues on the isolated rat stomach strip preparation, Brit. J. Pharmacol. 14, 87 (1959).

Vane, J.R., The actions of sympathomimetic amines on tryptamine receptors, in Vane, J.R. (ed.) Adrenergic Mechanisms, Ciba Foundation Sympos., p. 356, Churchill, London, 1960.

Weinstein, H., Maayani, S., Srebrenik, S., Cohen, S. and Sokolovsky, M., Psychotomimetic drugs as anticholinergic agents II. Quantum-mechanical study of molecular interaction potentials of 1-cyclohexylpiperdine derivatives with the cholinergic receptor, Mol. Pharmacol. 9, 820 (1973).

Weinstein, H., Srebrenik, S., Paunz, R., Maayani, S., Cohen, S. and Sokolvsky, M., Characterization of drug reactivity in cholinergic systems by molecular interaction potentials, in Bergmann, E.D. and Pullman, B. (ed.), p. 493, Chemical and Biochemical Reactivity, Israel Acad. Sci., Jerusalem, 1974.

Weinstein, H., Maayani, S., Srebrenik, S., Cohen, S. and Sokolovsky, M., A theoretical and experimental study of the semirigid cholinergic agonist 3-acetoxyquinuclidine, Mol. Pharmacol. 11, 671 (1975).

Weinstein, H., Chou, D., Johnson, C.L., Kang, S. and Green, J.P., Tautomerism and the receptor action of histamine: a mechanistic model, Mol. Pharmacol. 12, 738 (1976a).

Weinstein, H., Chou, D., Kang, S., Johnson, C.L. and Green, J.P., Reactivity characteristics of large molecules and their biological activity: indolealkylamines on the LSD/serotonin receptor, Int. J. Quantum Chem. (1976b).

Whittaker, V.P., Michaelson, J.A. and Kirkland, R.J.A., The separation of synaptic vesicles from nerve ending particles ("synaptosomes"), Biochem. J. 90, 293 (1964).

Winter, J.C. and Gessner, P.K., Phenoxybenzamine antagonism of tryptamines, their indene isosteres and 5-hydroxytryptamine in the rat stomach fundus preparation, J. Pharmacol. Exp. Therap. 162, 286 (1968).

Winter, J.C., Gessner, P.K. and Godse, D.D., Synthesis of some 3-indenealkylamines and 3-benzo[b]thiophenealkylamines with their tryptamine isosteres, J. Med. Chem. 10, 856 (1967).

Yunger, L.M. and Harvey, J.A., Kinetic analysis of ^{3}H-serotonin accumulation in four regions of rat brain after lesions in the medial forebrain bundle, Life Sci. 19, 105 (1976).