Comparison of Phencyclidine and Related Substances With Various Indole, Phenethylamine, and Other Psychotomimetics[1,2]

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Introduction

Psychotomimetics are logically classified on the basis of chemical structure. They include: 1) Indolealkylamines such as tryptamine, dimethyltryptamine (DMT), 5-methoxydimethyltryptamine (5-MeODMT), psilocin, etc. 2) Lysergic acid amides (also called lysergimides) such as lysergic acid diethylamide-25 (LSD-25) or LSD for short. LSD contains an indole structure and is frequently classified as an indole hallucinogen. However, its more complex chemical structure warrants a separate classification. Furthermore, it is much more difficult to synthesize and therefore to obtain illicitly. 3) Some of the phenethylamines, including amphetamine-like compounds (amphetamine, *p*-methoxyamphetamine, methamphetamine), and mescaline-like compounds [mescaline, 2, 5-dimethoxy-4-methylamphetamine (DOM), methylenedioxyamphetamine (MDA)]. 4) Infrequently abused are the M-cholinergic antagonists such as atropine and 3-quinuclidinyl benzilate (QNB). The latter is also known as BZ and at one time was proposed as a chemical warfare agent to induce a psychotomimetic state. 5) Still another class of psychotomimetic agents is the arylcyclohexylamines such as phencyclidine (PCP). At least five chemical subtypes include PCP-like compounds, dioxalanes, benzomorphans, and unbridged and bridged benz(f)isoquinolines, all of which have been called "phencyclinoids" and/or "*sigma*" opioids (for SKF 10,047). Substances with other heterocyclic structures also produce psychotomimetic effects including 6) cannabinoids like Δ^9-THC, the active ingredient in marijuana, 7) β-carbolines like harmine and harmaline, 8) some of the constituents of nutmeg including myristicin and elemicin, and 9) catatonic producing agents such as bulbocapnine.

Prototypic Chemical Structures of Various Substances Showing PCP-Like Activity

As mentioned above, a number of chemicals with different molecular structures have PCP-like effects. All of these have been tested in animals. Only some of these have been verified to be similar in man. The compounds with prototypic structures include those shown in Figure 1. An important chemical problem is to establish the absolute configuration of all of these substances to determine the common elements shared with PCP itself. To make matters even more complex, PCP exists in four different conformations as shown in Figure 2.

This has prompted Kamenka (1983) to use the term "chameleon" in describing the PCP molecule and its four different conformations. Which is the active conformation in the PCP receptor complex?

Mechanism of Action of Psychotomimetic Agents

An important book which summarizes some of our knowledge on the neurochemical, behavioral, and clinical perspectives of hallucinogens is that edited by Jacobs (1984). With so many diverse chemical classes of psychotomimetics, there is no simple unifying theory as to how they act. Most investigators feel that the major chemical messengers in the brain including norepinephrine (NE), dopamine (DA), serotonin (5-HT), acetylcholine

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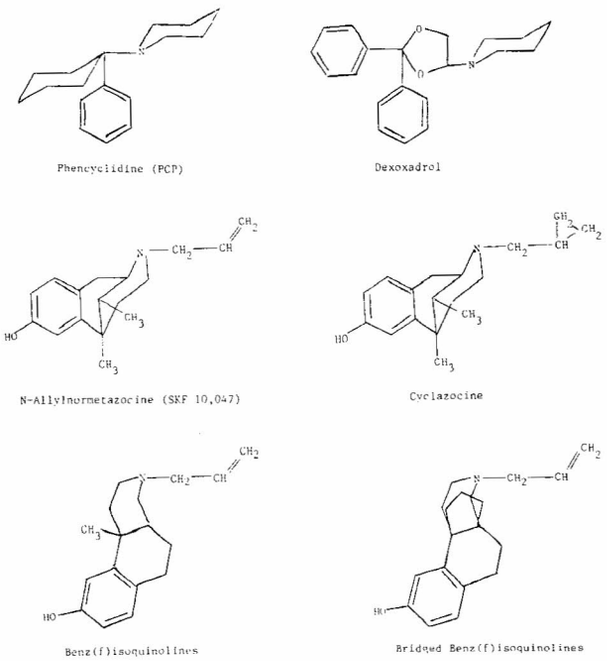

FIGURE 1. Chemical structures of various compounds that have phencyclidine-like activity.

(ACh), and some excitatory amino acids like glutamate, in particular, N-methylaspartate (NMA), are involved. The two catecholamines, DA and NE, along with the trace brain amines phenethylamine and phenethanolamine, appear to be most implicated with stimulant-induced psychoses such as those produced by amphetamine, methamphetamine, etc.

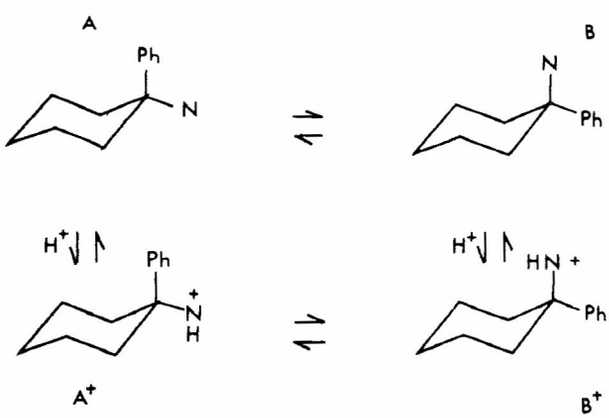

FIGURE 2. PCP exists in four different conformations.

On the other hand, other phenethylamines such as mescaline, DOM, and various indolealkylamine and lysergic acid amides, appear to involve the chemical messenger 5-HT. The newer developments in this field relate to the subtypes of 5-HT receptors. Ligand binding assays using *in vitro* brain membrane fractions from animals are now widely used by neuroscientists. LSD-25 binds to both 5-HT_1 and 5-HT_2 receptors as do some nonhallucinogenic ergot analogs like lisuride. However, almost all of these two classes of hallucinogens seem to interact more on 5-HT_2 sites (Peroutka & Snyder, 1983; Shannon et al., 1984). Shannon et al. (1984) used radiolabeled ^{3}H-5-HT and ^{3}H-ketanserin to label 5-HT_1 and 5-HT_2 sites, respectively. They found that among the various hallucinogens studied (especially phenethylamine derivatives which can be further subclassified as phenisopropylamines) that radioactive binding was more stereoselective to 5-HT_2 than 5-HT_1 sites. Furthermore, the 5-HT_2 binding affinities (called K_i values) of those hallucinogens correlated with rat behavioral discriminative data (effective dose 50 percent or ED50s). In turn, these correlated with the potencies of some of these compounds as hallucinogens in man.

About 20 years ago, it was discovered that animals, when properly trained, discriminate the effects of drugs. Ho et al. (1978), Colpaert and Rosecrans (1978), and Colpaert and Slangen (1982) organized symposia that have summarized much of our knowledge in this field. A given class of drugs such as LSD has discrete stimulus properties that can be distinguished from another unrelated class (Δ^9-THC, etc). Furthermore, animals such as rats can be trained to distinguish morphine from 0.9 percent NaCl placebo from LSD-25, etc. Appel et al. (1982) and Appel and Rosecrans (1984) have reviewed the behavioral pharmacology of hallucinogens in animals on respondent (pavlovian) conditioning and operant (instrumental) conditioning. They point out that the most highly specific operant paradigm to distinguish hallucinogens is drug discrimination. They reviewed the evidence for a common 5-HT_2 and/or hallucinogen receptor mode of action for a variety of compounds. Rech and Commissaris (1982)

additionally have provided evidence that a particular spectrum of activity at 5-HT_2 relative to 5-HT_1 receptor sites is characteristic of a large variety of hallucinogens.

Jacobs (1984) summarized the evidence that hallucinogens such as DMT, DOM, LSD-25, mescaline, and psilocybin act on postsynaptic 5-HT receptors. All of these compounds elicit a so-called "5-HT behavioral syndrome" in rats which consists of head weaving, tremor, rigidity, Straub tail, splayed hindlegs, and forepaw treading. Tolerance and cross-tolerance to these effects are observed which correlate with decreases (down-regulation) of 5-HT binding sites. Jacobs (1984) has provided evidence that the behavioral effects of such 5-HT acting hallucinogens can be dissociated from their presynaptic actions on 5-HT neurons.

Can the actions of LSD-25 and related indole and phenethylamine hallucinogens on the 5-HT system be related to the actions of arylcyclohexylamines such as PCP or to psychomotor stimulants like amphetamine? Probably not, but there are some interesting relationships and contrasts. Most psychotomimetics, when given chronically, induce tolerance. On the other hand, in rodents chronic amphetamine effects are potentiated. In other words, chronic use produces supersensitivity. Nabeshima and his colleagues in Japan (1985) have shown that PCP given chronically to rats produces a mixed picture. The PCP-induced "5-HT like syndrome" is attenuated with chronic PCP administration and shows cross-tolerance to 5-MeODMT, while DA mediated behavioral effects such as sniffing, rearing, or licking are enhanced in chronic PCP treated rats given PCP or DA agonists such as apomorphine and methamphetamine. Thus, tolerance is observed in the 5-HT mediated but not the DA mediated effects of PCP. The conclusions by Nabeshima and colleagues are only partially in agreement with those of Greenberg and Segal (1985). The latter found that the acute co-administration of amphetamine and PCP increased only stereotypy, a classic DA mediated behavior. On the other hand, although chronic administration of both drugs separately produced enhanced locomotor stimulation, the chronic PCP treated rats showed a decreased response to amphetamine, indicating different mechanisms underlie the effects of acute and chronic administration of both drugs.

Perhaps the most important new development in the mechanisms of action of PCP involves its effects on excitatory amino acid neurotransmitter systems. It has long been known that PCP in receptor, binding assays acts on the muscarinic cholinergic receptor, on the *delta* subunit of the ion channel of the nicotinic receptor, and on various Ca^{++} and K^+ ion channels (*see* Domino, 1981; Kamenka et al., 1983). Lodge et al. (1982, 1983) and Anis et al. (1983) were the first to show that arylcyclohexylamines including ketamine, PCP, tiletamine, and etoxadrol selectively reduced excitation of mammalian neurons by NMA, but not by quisqualate and kainate. Subsequently, Snell and Johnson (1985, 1986) reported that several substances with PCP-like behavioral effects inhibited the release of two chemical messengers, ACh and DA, evoked by NMA from rat striatal slices *in vitro*. They also showed that these effects were similar to the classic NMA antagonist, 2-amino-5-phosphonovalerate, except that the latter produced a parallel shift to the right in the concentration effect curve, while PCP produced a non-parallel shift to the right, suggesting a noncompetitive interaction between PCP and NMA. Koek et al. (1986) have used a behavioral analysis in animals regarding PCP and its interaction with NMA. They suggest that this might be important in the mechanisms of anesthesia induced by arylcyclohexylamines and related substances.

Conclusions

PCP-like compounds appear to possess a unique wide spectrum of pharmacological effects. Their mechanisms of action are as yet unknown, but clearly appear to be different from other major classes of psychotomimetic agents.

References

Anis, N.A., Berry, S.C., Burton, N.Y., and Lodge, D. The dissociative anaesthetics, ketamine and phencyclidine selectively reduce excitation of central

mammalian neurones by N-methyl-aspartate. *Br. J. Pharmacol.*, 79:565–575, 1983.

Appel, J.B., White, F.J., and Holohean, A.M. Analyzing mechanism(s) of hallucinogenic drug action with drug discrimination procedures. *Neuroscience and Behavioral Reviews,* 6:529–536, 1982.

Appel, J.B., and Rosecrans, J.A. Behavioral pharmacology of hallucinogens of animals: Conditioning studies. In: Jacobs, B.L., (ed.), *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives*. New York: Raven Press, 1984, pp. 77–94.

Colpaert, F.C., and Rosecrans, J.A., eds. *Stimulus Properties of Drugs: Ten Years of Progress*. Amsterdam: Elsevier, 1978, 572 pp.

Colpaert, F.C., and Slaugen, J.F., eds. *Drug Discrimination: Application in CNS Pharmacology*. Amsterdam: Elsevier, 1982, pp. 1–447.

Domino, E.F., ed. *PCP (Phencyclidine): Historical and Current Perspectives*. Ann Arbor, MI: NPP Books, 1981, 537 pp.

Greenberg, B.D., and Segal, D.S. Acute and chronic behavioral interactions between phencyclidine (PCP) and amphetamine: Evidence for a dopaminergic role in some PCP-induced behaviors. *Pharmacol. Biochem. Behavior,* 23:99–105, 1985.

Ho, B.T., Richards, D.W., and Chute, D.L. *Drug Discrimination and State Dependent Learning*. New York: Academic Press, 1978, pp. 1–392.

Jacobs, B.L., ed. *Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives*. New York: Raven Press, 1984. 233 pp.

Kamenka, J.M., Domino, E.F., and Geneste, P., eds. *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*. Ann Arbor, MI: NPP Books, 1983, 660 pp.

Koek, W., Kleer, E., Mudar, P.J., and Woods, J.H. Phencyclidine-like catalepsy induced by the excitatory amino acid antagonist DL-2-amino-5-phosphonovalerate. *Behav. Brain Res.* (In press, 1986.)

Lodge, D., Anis, N.A., and Burton, N.R. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurons by amino acids and acetylcholine. *Neurosci. Lett.*, 29:282–286, 1982.

Lodge, D., Anis, N.A., Berry, S.C., and Burton, N.R. Arylcyclohexylamines selectively reduce excitation of mammalian neurons by aspartate-like amino acids. In: J.M. Kamenka, E.F. Domino, and P. Geneste (eds.), *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*. Ann Arbor, MI: NPP Books, 1983, pp. 595–616.

Nabeshima, T., Yamaguichi, K., Hiramatsu, M., et al. Development of tolerance and supersensitivity in rats treated with phencyclidine (PCP) chronically. *Personal Communication to E.F. Domino*, December, 1985.

Peroutka, S.J., and Snyder, S.H. Multiple serotonin receptors and their physiological significance. *Federation Proc.*, 42:213–217, 1983.

Rech, R.H., and Commissaris, R.L. Neurotransmitter basis of the behavioral effects of hallucinogens. *Neurosci. Biobehav. Rev.*, 6:521–527, 1982.

Shannon, M., Battaglia, G., Glennon, R.A., and Titeler, M. 5-HT_1 and 5-HT_2 binding properties of derivatives of the hallucinogen 1-(2,5-dimethoxy-phenyl)-2-aminopropane (2,5-DMA). *Eur. J. Pharmacol.*, 102:23–29, 1984.

Snell, L.D., and Johnson, K.M. Antagonism of N-methyl-D-aspartate induced transmitter release in the rat striatum by phencyclidine like drugs and its relationship to turning behavior. *J. Pharmacol. Exp. Ther.*, 235:50–58, 1985.

Snell, L.D., and Johnson, K.M. Characterization of the inhibition of excitatory amino acid induced neurotransmitter release in the rat striatum by phencyclidine-like drugs. *J. Pharmacol. Exp. Ther.* (In press, 1986.)