corneal reflexes returned, ventilation was halted and the heart fibrillated with an electrical stimulus. After 10 minutes of cardiac arrest, ventilation was restored, internal cardiac compressions maintained MAP>100 mmHg while 40 μg/kg epinephrine, 20 mg/kg lidocaine, 4 meq/kg sodium bicarbonate, and 25 mg/kg calcium chloride were administered IV. Cardioconversion was accomplished by delivering a 80 watt second charge directly to the myocardium. Ketamine administration was started via saphenous vein as 0.5 mg/kg slow bolus and 1.7 mg/kg 1.5 hr infusion. The chest was closed and the dogs breathed unassisted. Neurologic deficit was scored (range: 0=no deficit, 100=profound deficit or death) at 1, 2, 6, 12, and 24 hours post cardiac arrest. Animals receiving ketamine (n=7) required less epinephrine to maintain MAP>75 mmHg (p=0.010) and less lidocaine (p=0.052) to treat arrhythmias than control animals (n=8). Ketamine-treated dogs also had a significantly higher MAP at 7 hours (p=0.017), 18 hours (p=0.020), and 24 hours post arrest (p=0.05) with lower HR at all times.

	1 Hour	2 Hour	6 Hour	12 Hour	24 Hour
Control	64.4±2.1	62.0±2.43	56.1±6.1	65.4±15.6	90.4± 9.6
Ketamine	59.6±1.8	60.0±2.6	35.0±6.3	21.9± 3.6	53.3±16.9
p value	0.1087	0.5654	0.0323	0.0095	0.0702

Ketamine dogs had a consistently lower deficit at all scoring times, and this difference was statistically significant at 6 and 12 hours as indicated by p values for the Student t test. These data suggest that IV ketamine administration, at human anesthetic doses, leads to the reduction of neurologic deficit following a global cerebral ischemic insult.

INTERACTIONS BETWEEN PHENCYCLIDINE AND NMDA RECEPTORS: EVIDENCE FOR A GABA-BENZODIAZEPINE-LIKE SUPRAMOLECULAR COMPLEX.

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Early studies by Lodge *et al.* demonstrated that phencyclidine and ketamine are non-competitive NMDA antagonists using electrophysiological techniques. We propose that receptors for these compounds form a supramolecular complex to regulate an ion channel, in a manner analogous to the GABA-BZ receptor complex. Recent behavioral, physiological and biochemical studies in our laboratories investigated the interactions of the PCP and NMDA binding sites. Behavioral studies demonstrated that PCP and competitive NMDA excitatory amino acid antagonists, such as APH, have similar or identical actions of PCP and APH. Similar conclusions were reached in studies on ischemic effects in primary cultures of hippocampal neurons. Taken together, these data indicate that PCP modulates the NMDA excitatory amino acid receptor and associated sodium channel in much the same way that benzodiazepines modulate the GABA inhibitory amino acid receptor and associated chloride channel. Both of these systems also seem to have endogenous peptide ligands regulating the modulatory sites. The work of Guidotti *et al.* demonstrated the existence of diazepam binding inhibitor which negatively modulates the GABA site through its interactions with the benzodiazepine site. Similarly, α-endopsychosin (DiMaggio *et al.* this symposium) may negatively modulate the NMDA site through its interaction with the PCP receptor.

*Deceased.

THE SEARCH FOR A PHENCYCLIDINE (PCP) ANTAGONIST. PCP-LIKE EFFECTS OF A SERIES OF SUBSTITUTED DIOXOLANES RELATED TO DEXOXADROL.

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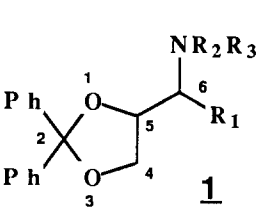
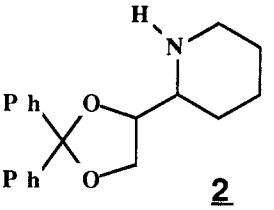
Phencyclidine (PCP) was originally developed as an anesthetic, however, its use in man was limited by disturbing psychotomimetic side-effects, often resembling acute schizophrenia. PCP-like behavioral effects were also observed in man with dexoxadrol. Based on this evidence, it was proposed that a PCP antagonist might serve as a novel antipsychotic drug. As a part of our program to develop a PCP antagonist and evaluate the unique pharmacological potential of such a compound, we explored the structural requirements for activity in a series of dioxolane derivatives (1) related to dexoxadrol (2).



1



2

Our SAR centered around the acyclic derivative 1. We varied the substitution on the carbon (C_6) adjacent to the nitrogen (R_1=H, alkyl, aralkyl, phenyl), while maintaining the dexoxadrol relative stereochemistry at C_5 and C_6. We also varied the substituents on the nitrogen (R_2 and/or R_3=H, alkyl, aralkyl). All products were assayed using methods directed towards showing PCP agonist as well as antagonist activity. The affinity of these compounds for the PCP receptor was determined from the ability of these compounds to inhibit ^{3}H-PCP binding. Agonist-like activity could be demonstrated by examining the ability of these compounds to produce PCP-like catalepsy in pigeons. Compounds that bound to the PCP receptor but did not cause catalepsy were then subsequently examined for their ability to block PCP-induced catalepsy in pigeons. As another assay of PCP-like agonist activity, some compounds were tested for their ability to block N-methyl-D-aspartate-induced lethality in mice. The full extent of these results and the chemical methods to prepare these compounds will be discussed.

METABOLISM OF PHENCYCLIDINE AND ITS OXIDATION PRODUCT, THE IMINIUM COMPOUND, LEADS TO DESTRUCTION OF SPECIFIC RABBIT LIVER MICROSOMAL P-450 CYTOCHROMES.

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In studies on the interaction of purified P-450 cyto-

chromes with various xenobiotics, the effects of phencyclidine (PCP) were examined. The formation of a reactive iminium ion from PCP, as well as the covalent binding of PCP metabolites to proteins and the inhibition of N-demethylase activity in the microsomal system by PCP have previously been reported by others (Hoag, M. K. P., A. J. Trevor, Y. Asscher, J. Weissman and N. Castagnoli. *Drug Metab Disp* **12:** 371–375, 1984. Ward, D. P., A. J. Trevor, A. Kalir, J. D. Adams, T. A. Baillie and N. Castagnoli. *ibid.* **10:** 690–695, 1982). We have found that PCP selectively inactivates P-450 form 2, the major phenobarbital-inducible isozyme from rabbit liver microsomes, in a reconstituted system containing NADPH-cytochrome P-450 reductase, phosphatidylcholine, and an NADPH-generating system. Aliquots were taken over time from this mixture, diluted 20-fold, and assayed for 7-ethoxycoumarin deethylase activity, Time-, NADPH-, and PCP concentration-dependent inhibition of deethylase activity were observed. The kinetics are indicative of a biphasic first order process with rate constants of 0.43 and 0.07 min^{-1} for the fast and slow phases, respectively. The iminium intermediate (kindly provided by Drs. Hoag, Trevor, and Castagnoli) also inactivated isozyme 2 at a similar rate, but was less selective, for it also inhibited constitutive cytochrome P-450, form 3b. PCP and the iminium ion had little or no effect on ethanol-inducible P-450 form 3a, 3-methylcholanthrene-inducible form 4, or tetrachlorodibenzo-*p*-dioxin-inducible form 6. PCP caused little or no change in P-450-mediated activities in intact microsomes, due mainly to the presence of P-450s other than form 2; furthermore, titration with anti-form 2 antibody of the residual microsomal activity after PCP treatment indicated that no other forms were affected. The loss of the Soret absorption band and of the ability to form the ferrous carbonyl complex and the pyridine hemochrome complex indicates modification of the heme moiety. Experiments are in progress with tritiated PCP to elucidate further the nature of its interaction with P-450 heme and apoprotein. (Supported by NIH grant DK-10339.)

MOLECULAR CRITERIA FOR AN IMMUNOLOGICAL MODEL OF THE PCP RECEPTOR. Owens, S. M., M. Zorbas, M. Gunnell, M. Polk and D. L. Lattin. Department of Pharmacology and Interdisciplinary Toxicology and Department of Biopharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, AR 72205.

A series of antibodies against PCP derivatives were generated in rabbits to determine the molecular requirements for an immunological model of the PCP receptor. Three different antibodies were produced against the PCP molecule by immunization with haptens covalently bound to bovine serum albumin (BSA) off of the para position of each of the three ring structures of PCP (i.e., aromatic, cyclohexane and piperidine rings). A fourth antibody was produced by immunization with BSA coupled to the PCP metabolites, PCHAP (5-[N-(1'-phenylcyclohexyl)amino]pentanoic acid). The antigen for this fourth antibody was designed to produce antibodies that would be highly cross-reactive with the potent PCP analogue, PCE (N-ethyl-1-phenylcyclohexylamine). The cross-reactivity patterns of all four antibodies were then determined in a radioimmunoassay (RIA) format using ^{3}H-PCP and numerous PCP analogues. The relative potencies of these antibodies, determined from IC_{50} values, were then correlated with relative potency data from receptor binding studies (Quirion *et al.*, 1983) and from discriminative stimulus studies in the rat (Shannon, 1981). There was a significant correlation between the PCHAP RIA data and the receptor binding data ($r=0.89$; $p<0.005$), and between the PCHAP RIA data and the discriminative stimulus data ($r=0.89$; $p<0.005$). Since none of the other antibodies showed any correlation with the relative potency data from receptor binding or behavioral studies, the PCHAP antibody appears to be the best immunological model for the PCP receptor. In related studies, the antigens used for the production of the antibodies were used as ligands in a ^{3}H-PCP neuroreceptor binding assay. The PCHAP antigen was found to be the most potent antigen for inhibition of ^{3}H-PCP binding. These studies represent preliminary evidence that an immunological model can be developed for the PCP neuroligand binding site. (Supported by NIDA grant DA 04136 and NIDA Research Scientist Development Award (S.M.O.) KO2 DA00110.)

EFFECTS OF PHENCYCLIDINE HYDROCHLORIDE ON NEUROENDOCRINE FUNCTION IN THE RAT. Pechnick,* R. N., R. George* and R. E. Poland.† *Department of Pharmacology, U.C.L.A. School of Medicine, Los Angeles, CA 90024; and †Division of Biological Psychiatry, Harbor-U.C.L.A. Medical Center, Torrance, CA 90502.

Phencyclidine (PCP) is a widely used drug of abuse; however, little is known of the effects of PCP on neuroendocrine function. We have previously reported that the acute administration of PCP produced increased serum levels of corticosterone in the rat (*Life Sci* **38:** 291–296, 1986), but it is not known whether this effect is due to a direct effect on the adrenal or is mediated via increased release of adrenocorticotrophin (ACTH) from the pituitary. The purpose of the present study was to determine the effects of the acute administration of PCP on the release of ACTH, and in addition, luteinizing hormone (LH) in the rat. Male rats were injected SC with saline or varying doses of PCP, and trunk blood was obtained at 15, 30, 60, 120, and 180 min after injection. Plasma levels of ACTH and LH were measured by radioimmunoassay. PCP increased plasma levels of ACTH 15 min after administration, and ACTH levels remained significantly elevated 180 min after injection with the higher doses. In contrast, PCP decreased serum levels of LH; however, this effect was not observed until 180 min after injection. These findings indicate that PCP is a potent releaser of ACTH but inhibits the release of LH in the rat. (Supported by NIDA grant DA-04113.)

EVIDENCE FROM 2-DG AUTORADIOGRAPHY THAT PHENCYCLIDINE'S FUNCTIONAL EFFECTS ARE MEDIATED BY SPECIFIC PCP RATHER THAN SIGMA RECEPTORS. Piercey, M. F., C. Ray and G. D. Vogelsang. CNS Research, The Upjohn Company, Kalamazoo, MI 49001.

Sokoloff's 2-deoxyglucose (2-DG) autoradiographic technique (*J Neurochem* **28:** 897, 1977) was used to identify neural structures underlying the behavioral effects of phencyclidine (PCP) and to compare the distribution of PCP's