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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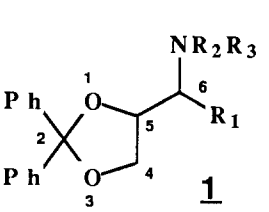
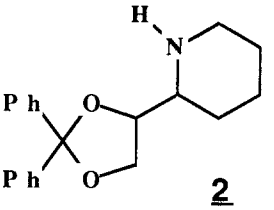
Phencyclidine (PCP) was originally developed as an anesthetic, however, its use in man was limited by disturbing psychotomimetic side-effects, often resembling acute schizophrenia. PCP-like behavioral effects were also observed in man with dexoxadrol. Based on this evidence, it was proposed that a PCP 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-