PHENCYCLIDINE AND CEREBRAL CYTOCHROME P-450. Minn, A., B. Walther, R. Perrin, J. F. Ghersi-Egea, J. M. Ziegler and G. Siest. Université de Nancy I, Centre du Médicament, U.A. CNRS No. 597, 30 rue Lionnois, 54000 Nancy, France.

The cytochrome P-450 linked monooxygenase system (P-450) is responsible for the NADPH-dependent oxidation of a wide variety of lipophilic xenobiotics and endogenous substrates. Previous studies indicated that PCP undergoes extensive biotransformation in the liver with major group of metabolites derivated from aromatic hydroxylation and opening of the piperidine ring, these reactions being the result of P-450 activity (Kalir *et al.*, 1983). We recently showed that cerebral P-450 is mainly localized in mitochondrial and microsomal fractions (Walther *et al.*, 1986). Although cerebral P-450 activity is relatively low, the cerebral drug metabolism may be of importance in the production of toxic or reactive metabolites and possibly in the formation of peculiar pharmacologically active molecules. When substrates, products or inhibitors interact with the active site of P-450, typical difference spectra occur. The incubation of PCP with brain mitochondrial or microsomal P-450 promoted a "type I" spectral modification, indicating that PCP interacts with the active site as a substrate for this enzyme. On the other hand, when PCP was added to brain microsomes incubated in the presence of NADPH, some hydroxylated metabolites may be identified in the incubation medium. These results support the possibility of a cerebral biotransformation of PCP. As the administration of various drugs to animals causes selective induction of one or two particular forms of P-450 depending on the drug administered and leading to the activation of drug metabolism, we studied the effect of a chronic PCP treatment (25 mg/kg daily IP, 7 days) on the brain enzyme levels. No significative changes in microsomal nor mitochondrial P-450 levels were observed in these conditions. Kalir, A., A. J. Trevor, D. P. Ward, J. D. Adams, T. A. Baillie and N. Castagnoli. Reactive metabolites of phencyclidine and covalent binding to microsomal proteins. In: *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*, edited by J. M. Kamenka, E. F. Domino and P. Geneste. Ann Arbor: NPP Books, pp. 267–277, 1983. Walther, B., J. F. Ghersi-Egea, A. Minn and G. Siest. Subcellular distribution of cytochrome P-450 in the brain. *Brain Res* **375:** 338–344, 1986.

PROPERTY OF PHENCYCLIDINE AS A 5-$HT_2$ RECEPTOR AGONIST. Nabeshima, T., K. Ishikawa, K. Yamaguchi, H. Furukawa* and T. Kameyama. Department of Chemical Pharmacology and *Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan.

Phencyclidine (PCP)-induced stereotyped behaviors including head-weaving, turning and backpedalling are mediated by serotonergic neurons, since the lesion of the striatum induced by a serotonergic neurotoxin, 5,6-dihydroxytryptamine, and the electrolytic lesion of the raphe nucleus which contains 5-HT cell bodies diminish PCP-induced behaviors (Nabeshima *et al.*, *Eur J Pharmacol* **91:** 455, 1983; ibid. **93:** 229, 1983). PCP interacts with the 5-$HT_2$ receptors, since it inhibits [3H]spiperone binding to 5-$HT_2$ receptors (Nabeshima *et al.*, *Res Commun Subst Abuse* **5:** 81, 1984; ibid. **5:** 175, 1984) and chronic administration produces down regulation of 5-$HT_2$ receptors (Nabeshima *et al.*, *Eur J Pharmacol* **109:** 129, 1985; ibid. **133:** 319, 1987). Methysergide inhibits the development of tolerance to PCP-induced head-twitch response, but not to head-weaving, turning and backpedalling. Methysergide protects [3H]ketanserin binding sites from the down regulation (Nabeshima *et al.*, *Eur J Pharmacol* **133:** 319, 1987). Furthermore, methysergide produces a precipitated withdrawal syndrome in PCP-tolerant rats (Nabeshima *et al.*, *Neurosci Lett* **69:** 275, 1986). Ritanserin, a selective 5-$HT_2$ receptor antagonist, antagonized the PCP-induced head-twitch responses in mice and rats (Nabeshima *et al.*, *Neurosci Lett*, in press, 1987). In the present experiments, we investigated whether PCP could protect the binding sites of [3H]PCP and [3H]ketanserin from an inhibitory effect of protein-modifying reagents which affect sulfhydryl groups. In the rat brain synaptic membrane, PCP (10 $\mu$M) provided a protection against inactivation of [3H]PCP and [3H]ketanserin binding sites induced by sulfhydryl reagents such as N-ethylmaleimide (NEM), iodoacetamide, 5,5'-dithiobis-(2-nitrobenzoic acid) and *p*-chloromercuribenzoate. Ritanserin (1 $\mu$M) also completely prevented the inhibitory action of NEM on [3H]PCP and [3H]ketanserin binding sites, but 5-HT (10 $\mu$M) failed to prevent it. 5-HT protected [3H]5-HT binding sites from the inactivation by NEM, but PCP and ritanserin did not show any effect. Scatchard plots of specific [3H]PCP and [3H]ketanserin binding showed that NEM (100 $\mu$M) caused a significant decrease in Bmax without changing Kd. Furthermore, PCP (10 $\mu$M) and ritanserin (1 $\mu$M) antagonized the decrease of [3H]PCP and [3H]ketanserin binding sites induced by NEM (100 $\mu$M). On the basis of the present findings, it is concluded that PCP has an ability as an agonist for 5-$HT_2$ receptors, and PCP binding sites overlap 5-$HT_2$ receptors. This work was supported in part by the Science Research Promotion Foundation of Japan Private School Promotion Foundation (#1986-11).

KETAMINE REDUCES NEUROLOGIC DEFICIT FOLLOWING 10 MINUTES OF CARDIAC ARREST AND RESUSCITATION IN CANINES. Natale, J. E., R. J. Schott and L. G. D'Alecy. Departments of Physiology and Surgery, The University of Michigan Medical School, Ann Arbor, MI 48109.

Ketamine HCl has been shown to minimize the acute excitotoxic action of glutamate on neuronal cells by non-competitive antagonism of the N-methyl-D-aspartate receptor. The augmented release of glutamate during ischemia leads to cell death due to excessive excitation in the midst of metabolic compromise. Ketamine was administered to canines following 10 minutes of cardiac arrest and resuscitation to determine whether ketamine administered following the arrest would attenuate ischemia-induced neurologic damage. Adult, male mongrel dogs (15–25 kg) were randomly assigned to either the ketamine treatment or vehicle control (0.9% NaCl) condition. During ventilation with 1.5% halothane and oxygen, catheters were introduced into the deep femoral artery and vein and jugular vein, and a left thoractomy was performed to expose the heart. Halothane and oxygen were replaced with room air ventilation. When

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.

O'Donohue,* T. L., P. C. Contreras, J. B. Monahan, L. M. Pullan, G. E. Handelmann, D. G. Roufa and T. H. Lanthorn. Searle Research & Development, Division of G. D. Searle & Co., c/o Monsanto Company, 700 Chesterfield Village Parkway, St. Louis, MO 63198.

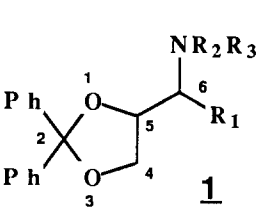
Early studies by Lodge *et al.* demonstrated that phencyclidine and ketamine are non-competitive NMDA antagonists using electrophysiological techniques. We propose that receptors for these compounds form a supramolecular complex to regulate an ion channel, in a manner analogous to the GABA-BZ receptor 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.

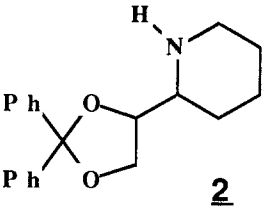
## THE SEARCH FOR A PHENCYCLIDINE (PCP) ANTAGONIST. PCP-LIKE EFFECTS OF A SERIES OF SUBSTITUTED DIOXOLANES RELATED TO DEXOXADROL.

Ornstein, P. L., D. M. Zimmerman, D. J. Leander, L. Mendelsohn, J. K. Reel and D. A. Evrard. Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

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.

Osawa, Y. and M. J. Coon. Departments of Biological Chemistry and Pharmacology, The University of Michigan, Ann Arbor, MI 48109-0606.

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