functional effects to the distribution of specific 'PCP' and sigma receptors, both of which bind PCP (Vignon *et al., Brain Res* **378:** 133, 1986). PCP, 5 mg/kg, was administered IP to male Sprague-Dawley rats 15 min prior to 25 μCi IV (^{14}C)-2-DG. Animals were sacrificed 45 min later. Autoradiograms of coronal sections were prepared from prefrontal pole to cervical cord. Computerized image analysis yielded quantitative measurements of regional energy metabolism. PCP dramatically increased metabolism in discrete brain regions, nearly all of which were located in diencephalic and telencephalic structures rich in PCP receptors (Largent *et al., JPET* **238:** 739, 1986). These effects were greatest in the limbic circuit described in 1937 by Papez (mammillary bodies, anterior thalamus, cingulate gyrus, entorhinal cortex, hippocampus, fornix), which was dramatically excited throughout, and the terminal zones of dopaminergic projections (caudate, n. accumbens, olfactory tub., prefrontal cortex). In general, anterior cortical regions, (especially sensory-motor cortex), were only weakly stimulated or even depressed, compared to more caudal cortical zones, (particularly striate 18), giving rise to an anteroposterior gradient similar to that reported in schizophrenia. Brainstem areas rich in sigma receptors (Largent *et al., ibid)* were generally unaffected. The inferior colliculus and the lateral habenula were inhibited. Chi-square analysis revealed a strong positive correlation for the areas stimulated with the presence of PCP receptors and a negative correlation with the presence of sigma receptors. Stimulated areas lacking PCP receptors (mamm. bodies, SNPR) had strong neuronal links to areas having high levels of PCP receptors. Haloperidol (HAL), which binds to sigma but not PCP receptors, antagonized PCP's stimulant effects in most dopaminergic areas, but not in Papez' circuit. Even HAL's effects were negatively correlated with the presence of sigma receptors. HAL tended to depress PCP's cortical stimulation throughout without altering the anteroposterior gradient; indeed, some anterior cortical regions were severely depressed below controls. HAL did not significantly affect PCP's intense cingulate stimulation. Although HAL stimulated the lateral habenula, it only partially reversed the depression evoked by PCP. It is concluded that PCP elicits its extreme psychotropic effects by intense stimulation of Papez' limbic circuit and dopamine release, all of which are probably mediated either directly or indirectly through the PCP receptor.

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP MODEL FOR PHENCYCLIDINE (PCP) COMPOUNDS. Pirat,* J. L. and J. M. Kamenka. Laboratoire de Chimie Organique Physique Appliquée and LP 8402-U 249, Ecole Nationale Supérieure de Chimie, 8, rue de l'Ecole Normale, Montpellier Cédex-France; Arnone, M. and M. Morre. Sanofi Recherche, Toulouse, France.

From previous results in our laboratory and others, modifications on the aromatic ring of the PCP molecule appear to influence biological activity *in vitro* and *in vivo*. Additionally, substitutions on the cyclohexyl moiety could contribute to an increase in PCP-like properties. To test this hypothesis, a model equation was generated for a structure with an intact phenyl group using the following parameters: steric-crowding (length), lipophilicity (Rekker's parameter), conformation and affinity for the ^{3}H-PCP receptor. This chemical model N-(phenyl-3,4-dimethylcyclohexyl) piperidine *cis* [2] was synthesized and tentatively improved by aromatic and piperidinic substitutions by a synthetic pathway to [2] via a classical Bruylants reaction on the suitable nitrile compound. Surprisingly we obtained stereoisomeric pairs although the Bruylants reaction has been generally regarded as stereospecific. Thirty new compounds were isolated and their structure characterized by ^{13}C NMR. Their binding properties were tested in competition with ^{3}H-PCP on guinea pig brain membranes. Few compounds exhibited affinities in the range of that for PCP. The mouse rotarod test did not show typical ED_{50}/IC_{50} relationships. The ED_{50} values were generally much higher than expected. However, behavioral evidence for antagonist properties was not found. Although the molecules obtained are related to PCP at the molecular level they seem to be devoid of agonist or antagonist properties in the behavioral test. It can be concluded that the cyclohexyl ring may play a role in the modulation of the biological activity of the PCP structure but not in the specific enhancement of PCP-like activity. *Present address: Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0626.

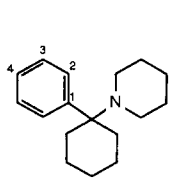
PHENCYCLIDINE AND NMDA—GLUTAMATE RECEPTORS IN HUMAN BRAIN. COMPARATIVE CHARACTERIZATION IN HUMAN BRAIN BIOPSIED TISSUES. Quirion, R., M. Dalpe, S. Lal, A. Olivier and M. Avoli. Douglas Hospital Research Centre and Montreal Neurological Institute, McGill University, Verdun, Quebec, Canada H4H IR3.

Much recent evidence has suggested that one class of glutamate receptor sites, namely the N-methyl-D-aspartic acid (NMDA) type, are closely associated to phencyclidine (PCP) receptors. Interestingly, it has recently been shown that both NMDA and PCP receptor sites are decreased in similar fashion in certain brain regions in Alzheimer's Disease (Maragos *et al., Trends Neurosci* **10:** 65–68, 1987). This supports the hypothesis of a close association between PCP and NMDA receptor sites and suggests possible involvement of these systems in the pathophysiology of Alzheimer's Disease. However, another study has shown that PCP and NMDA binding sites are only decreased in a sub-group of advanced Alzheimer patients (Monaghan *et al., Neurosci Lett* **73:** 197–200, 1987. This could be related to the different protocols used to characterize NMDA receptor type. Additionally post-mortem delays could generate certain artefacts that would be difficult to dissociate from the disease. To investigate this possibility, we report here on the comparative quantitative autoradiographic distribution of PCP and NMDA receptor binding sites in fresh human cortical biopsied tissues obtained following surgical removal in epileptic patients. Temporal cortex (outside epileptic foci) was obtained following partial lobectomy in few male epileptic patients between 35–50 years of age. The tissue was maintained once following surgery and then frozen on dry ice and kept at −70°C until used for quantitative autoradiography. On the day of the experiments, 20 μm thick adjacent brain cortex sections were incubated in presence of various concentrations of [^{3}H] TCP (Contreras *et al., Neurosci Lett* **67:** 101–106) or [^{3}H] L-glutamate (first series according to Monoghan *et al., Brain Res* **340:** 378–386, 1985; second series according to Maragos *et al., Eur J Pharmacol* **123:** 173–174, 1986) exactly as described before. Our results show that [^{3}H]

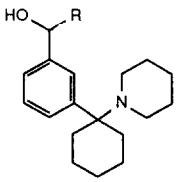
L-glutamate/NMDA-type binding sites are similarly distributed in human temporal cortex. The highest density of sites is found in superficial layers of the cortex while moderate and low densities are seen in deep and midlayers, respectively. Quantitatively, the maximal number of sites is generally slightly higher for NMDA sites suggesting that these receptors may not be exclusively and necessarily coupled or associated with PCP binding sites. We are currently investigating the respective alterations of these two classes of sites inside and outside active epileptic foci.

THE SEARCH FOR A PCP ANTAGONIST: SYNTHESIS AND CHARACTERIZATION OF NOVEL ARYLCYCLOHEXYLAMINE DERIVATIVES. Reel, J. K., L. G. Mendelsohn, J. D. Leander, D. M. Zimmerman, P. L. Ornstein, D. A. Evrard, D. D. Schoepp and R. B. Hermann. Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

Phencyclidine [1-(1-phenylcyclohexyl)piperidine, PCP], a major drug of abuse, initially had promise as a safe, general anesthetic. However, its use in man was precluded due to acute psychotic-like reactions. PCP is considered by many to be the best available drug model of schizophrenia and it is speculated that a specific antagonist for PCP may have useful antipsychotic activity; however, there are no reports of any compound having such antagonist activity. Consequently, we initiated a program in an attempt to discover a PCP antagonist. Incorporation of a hydroxyl group at the 2-and 4-position on the phenyl ring of PCP is known to reduce PCP receptor affinity while such substitution at the 3 position increases receptor affinity. These results prompted us to further investigate the effect of substitution at the 3-phenyl position. Compounds were evaluated for their affinity at the PCP receptor using a ^{3}H-PCP binding assay and for their ability to produce PCP-like catalepsy in pigeons. Novel compounds with high affinity and activity at the PCP receptor were discovered, including the 3-methanol analogs (1) where activity was maximized with R being hydrogen and phenyl. Three-dimensional molecular modeling procedures were used to compare 1 (R=phenyl) and dexoxadrol. These studies clearly showed that there was no energetically feasible way to superimpose the phenyl, oxygen and nitrogen moieties of these molecules.



PCP



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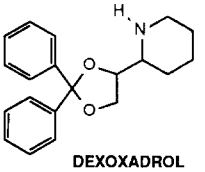

DEXOXADROL

ETOXADROL, A DIOXOLANE WITH PCP-LIKE ACTIVITY IN VIVO AND IN VITRO: SYNTHESIS, ABSOLUTE CONFIGURATION AND RECEPTOR BINDING STUDIES. Rice,* K. C., A. E. Jacobson,* A. Thurkauf,* M. Mattson,* E. L. May,† P. Zenk* and C. George.‡ National Institute of Diabetes, Digestive and Kidney Diseases, Bethesda, MD 20892, †Department of Pharmacology, Virginia Commonwealth University, Richmond, VA 23298 and ‡Naval Research Laboratory, Washington, DC 20375.

Dexoxadrol is unique among the four possible stereoisomers of this gross structure in that it binds to the PCP receptor and shows PCP-like behavioral effects in a number of systems. This high degree of stereoselectivity led us to recently determine the absolute configuration of dexoxadrol by single crystal x-ray analysis, and to propose two possible receptor-active conformations of this drug based on overlap of the piperidine ring and one of the phenyl rings with that of the corresponding features of PCP. The dioxolane etoxadrol shows a similar pharmacological profile to that of dexoxadrol but lacks one of the phenyl rings of the latter. Knowledge of the absolute configuration of etoxadrol together with inactivity of the ketal carbon epimer could reveal which of the phenyl rings of dexoxadrol is essential for PCP-like activity. Such data could also provide strong support for our proposal of the two possibilities for the receptor-active conformations of dexoxadrol. Structural determination of etoxadrol is now under investigation by single crystal x-ray analysis and our results to date will be reported. Mixtures of ketal carbon epimers isomeric with etoxadrol, have been prepared in the α-(−), β-(−), and β-(+) series (dexoxadrol nomenclature). Efforts are underway to obtain the corresponding epimer of etoxadrol, the eighth stereoisomer in this series. The affinity of these compounds for the PCP receptor will be discussed. We expect that when complete, this study will provide a much broader insight into rational design of new, high affinity ligands for the PCP receptor.

CHARACTERIZATION OF A NON-OPIOID SIGMA BINDING SITE IN GUINEA-PIG MYENTERIC PLEXUS. Roman, F., X. Pascaud, D. Vauche and J. L. Junien. Jouveinal Laboratoires, 1, rue des Moissons 94260 Fresnes, France.

On the basis of *in vitro* pharmacological and autoradiographic studies, Largent *et al.* have described the binding characteristics of (+)-[^{3}H]-SKF10,047 to guinea-pig and rat brain membranes (*J Pharmacol Exp Ther* **238:** 739, 1986). Little is known about the presence and the role of such *sigma*/PCP receptors in peripheral tissues. To our knowledge the only results on such *sigma* receptors in peripheral tissues have been reported by Samovilova *et al.* (*Bioorg Khim* **II:** 1380, 1985), using binding techniques on rat liver mem-