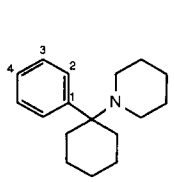
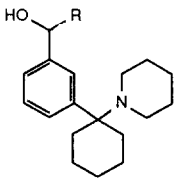
L-glutamate/NMDA-type binding sites are similarly distributed in human temporal cortex. The highest density of sites is found in superficial layers of the cortex while moderate and low densities are seen in deep and midlayers, respectively. Quantitatively, the maximal number of sites is generally slightly 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.

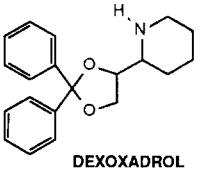
Phencyclidine [1-(1-phenylcyclohexyl)piperidine, PCP], a major drug of abuse, initially had promise as a safe, general anesthetic. However, its use in man was precluded due to acute psychotic-like reactions. PCP is considered by many to be the best available drug model of schizophrenia and it is speculated 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



(1)



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-