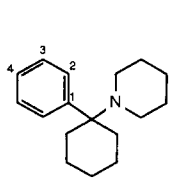
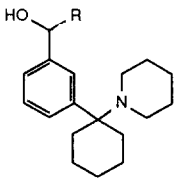
L-glutamate/NMDA-type binding sites are similarly distributed in human temporal cortex. The highest density of sites is found in superficial layers of the cortex while moderate and low densities are seen in deep and midlayers, respectively. Quantitatively, the maximal number of sites is generally slightly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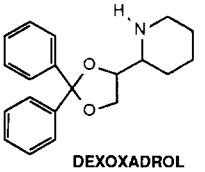

DEXOXADROL

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-

branes, whereas the effects of (+)-[^{3}H]-SKF10,047 on isolated guinea-pig ileum preparation have been described by Su *et al.* (*Life Sci* **28:** 2519, 1981), and Kromer *et al.* (*Naunyn Schmiedebergs Arch Pharmacol* **321:** 218, 1982). The present work was thus carried out in order to characterize binding sites for (+)-[^{3}H]-SKF10,047 in guinea-pig myenteric plexus membrane preparations. A saturable specific binding was found when (+)-[^{3}H]-SKF10,047 concentrations were increased from 1 to 50 nM. The equilibrium was reached in about 30 min. Dissociation was complete in 20–30 min. Specific binding was linear with protein concentration up to 1.2 mg/ml. In the range of concentrations explored, a binding site with K_D of 42.2±2.2 nM and a Bmax of 3.19±0.34 pmole/g tissue was determined from Scatchard plot. Morphine and naloxone were inactive up to 10^{-4} M. Among the other compounds tested, haloperidol, imipramine, ketocyclazocine and propranolol were the most potent to displace (+)-[^{3}H]-SKF10,047 from guinea-pig myenteric plexus membranes. In contrast PCP was much less active (IC_{50}=2.5 μM) a result which is at variance with those reported with guinea-pig whole brain membranes (IC_{50}=65 nM). These experiments suggest that *sigma* receptors are present in the guinea-pig myenteric plexus and put forward a putative physiologic role of *sigma* receptors at the gastrointestinal tract level.

PUTATIVE ROLE OF PCP-TCP RECEPTORS IN THE EFFECTS OF KINDLING. *Rondouin, G., I. Chaudieu, J. M. Kamenka and R. Chicheportiche. CNRS LP 8402-INSERM U 249, Ecole Nationale Superieure de Chimie, 8 rue de l'Ecole Normale, 34075 Montpellier Cedex, France; *Laboratoire de Medecine Experimentale, Bd Henri IV, 34060 Montpellier Cedex, France.

Phencyclidine (PCP) has been reported to delay the rate of kindling in rats. This drug and other *sigma* compounds were also reported to block long term potentiation, which mechanisms are partially related to those of the kindling effect. This study investigated the effects of thienylcyclidine (TCP) and some TCP derivatives in kindled rats. TCP and GK103 neither significantly reduced the duration of afterdischarges in kindled rats nor had a clear-cut anticonvulsant effect. The effects on behavioral stages of kindling were rather related to the ataxic effect of these two drugs. Conversely, GK115 blocked kindled seizures without producing an ataxic side-effect. Kindling also induced modifications in the binding parameters of ^{3}H-TCP, both in the cortex and in the cerebellum. These results will be discussed according to the multiple binding sites of these compounds.

THE RAT BRAIN PHENCYCLIDINE (PCP) RECEPTOR: A PUTATIVE K CHANNEL. Sorensen, R. G. and M. P. Blaustein. Department of Physiology, University of Maryland School of Medicine, Baltimore, MD 21201.

^{86}Rb efflux studies on rat brain synaptosomes (Bartschat and Blaustein, *PNAS* **83:** 189, 1986) show that PCP selectively blocks a voltage-dependent, non-inactivating K channel. This suggests that the brain PCP receptor may be associated with this K channel. The present study provides PCP receptor binding data which support this proposal. Aminopyridines (AP) and tetraalkylammonium ions (TAA), compounds which block voltage-dependent K channels, compete with [^{3}H]PCP for binding to rat brain synaptic membanes. Their orders of potency are: for the APs, 4-AP=3,4-diAP > 2-AP >> 3-AP, and for the TAAs, tetrabutylammonium (TBA) > tetraethylammonium > tetramethylammonium. These sequences agree with those reported for the ability of the APs and TAAs to block K channels or to increase neurotransmitter release (an effect which results from the block of K channels). The nature of the interactions of the APs and TAAs at the PCP receptor were further studied. Reciprocal and Schild plot analyses indicate that TBA is a competitive inhibitor at the PCP receptor. 4-AP has a more complex interaction, probably an allosteric inhibition: the results suggest that 2 mol of 4-AP are required to displace 1 mol of PCP at the receptor. These data show that K channel blockers interact directly with the brain PCP receptor. Additional data also implicate the PCP receptor as a K channel. One, the order of potency of PCP and several analogs for block of the synaptosome K channel, [TCP (thienyl analog) > m-amino-PCP > PCP > m-nitro-PCP], is the same as the order of affinities of these compounds for binding to the PCP receptor and for producing behavioral deficits. Two, the stereospecific binding of the "sigma" opiate, N-allylnormetazocine (NANM), [(+NANM > (−)NANM] and the dioxolane, dioxadrol, [dexoxadrol >> levoxadrol], to the PCP receptor are similar to those determined for their block of the synaptosome K channel. Reciprocal and Schild plot analyses demonstrate that (+)NANM and dexoxadrol are competitive inhibitors at the PCP receptor. Taken together, these results provide strong evidence that the brain PCP receptor is part of a K channel. We suggest that the behavioral deficit produced by PCP intoxication results from the ability of PCP to block this K channel. (Supported by NINCDS.)

STUDIES OF NEWER SYNTHETIC OPIOIDS: THE CARDIAC AND KINETIC EFFECTS IN CHILDREN AND PIGLETS. Stiller, R. L., P. J. Davis, D. R. Cook, M. D. Ingram, J. M. Perel and C. M. Roeber. Departments of Psychiatry, Anesthesiology and Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

Alfentanil (A), a structural analogue of fentanyl, is about