the United States. In man, PCP produces euphoria, dysphoria, excitation, ataxia, hallucinations and a schizophrenic-like psychosis. Most of the psychotomimetic effects of PCP are believed to be mediated by an interaction with specific PCP receptors. Until recently, it was thought that sigma opioids also interact with PCP receptors to produce dysphoria and hallucinations in man. Using ^{3}H-TCP (1-(1-(2-thienyl) cyclohexyl) piperidine) to label PCP receptors, and ^{3}H-(+)SKF 10,047 (N-allylnormetazocine), a sigma opioid, ^{3}H-haloperidol (in the presence of excess spiroperidol) and ^{3}H-(+)3PPP (N-n-propyl-3-(3-hydroxyphenyl)piperidine) to label sigma opioid binding sites, it was clear that PCP and sigma opioid binding sites were different. The rank order of potencies of several PCP analogs and sigma opioids for inhibiting the binding of ^{3}H-TCP was very different from that for inhibiting the binding of ^{3}H-(+)3PPP, ^{3}H-haloperidol or ^{3}H-(+)SKF 10,047. There were also differences in the anatomical distribution of PCP and sigma opioid binding sites. The physiological relevance of PCP binding sites is supported by the finding that the rank order of potencies for inhibiting the binding of ^{3}H-PCP is the same for inducing ataxia and stereotyped behavior in rats. The sigma opioids, cyclazocine and SKF 10,047, produced PCP-like stereotyped behavior and ataxia, but the sigma opioids also bind to the PCP receptor. Using selective ligands for the PCP, (MK-801) and sigma opioid (rimcazole and 1,3-di-o-tolyl-guanidine) binding sites should help determine the behavioral effects mediated by sigma opioid binding sites. MK-801, which has been reported to be noncompetitive antagonist at N-methyl-D-aspartate (NMDA) receptors, was found to bind potently to the PCP receptor with very little activity at the sigma binding site. In rats, MK-801 produced PCP-like stereotyped behavior and ataxia. PCP-like stereotyped behavior and ataxia was also produced by a competitive antagonist at the NMDA receptor. The (−) isomer of 2-amino-7-phosphonoheptanoate (AP7) was more potent that the racemic AP7 at binding to the NMDA receptor and producing stereotyped behavior and ataxia.

BIOLOGICAL AND CHEMICAL CHARACTERIZATION OF THE ENDOGENOUS ENDOPSYCHOSINS. DiMaggio, D. A., P. C. Contreras and T. L. O'Donohue. Department of Pharmacology, St. Louis, MO, and Division of CNS Research, Searle/Monsanto, St. Louis, MO.

Previous reports from our lab have demonstrated the existence of endogenous ligands for the phencyclidine (PCP) and the *sigma* receptors. The existence of two separate ligands supports previous data which indicate that the two receptors are distinct both in pharmacology and distribution. These endogenous ligands, which were isolated from preparative scale porcine brain acid extracts, have been designated *alpha-* and *beta*-endopsychosin. *Alpha*-endopsychosin inhibited the binding of ^{3}H-PCP to rat brain membranes in a selective and dose dependent manner, while *beta* endopsychosin selectively and specifically inhibited binding of ^{3}H-SKF 10,047 (N-allylnormetazocine), a sigma opioid, to rat brain membranes. The endopsychosins each have a distinct distribution in the CNS. Biological and chemical characteristics of the two ligands will be compared. Work done with antibodies generated against a sequenced portion of the beta ligand will be presented.

PCP AND ANALOGS SUPPRESS T LYMPHOCYTE PROLIFERATION BY PREVENTING THE MITOGEN-TRIGGERED RISE OF FREE CYTOSOLIC CALCIUM CONCENTRATION, A MESSAGE REQUIRED FOR IL-2 SYNTHESIS. Dornand, J., J. M. Kamenka* and J. C. Mani. CNRS ER228 and *CNRS LP8402, INSERM U249, ENSCM, Montpellier, France.

The psychotomimetic drug PCP displays a vast array of known pharmacological effects, among them is its capacity to affect cation transport in nervous and myocardiac tissues. Since increased movements of cations are essential for the immune responses, it has been mentioned that PCP and its analogue ketamine used for general anesthesia could also depress immune functions by this mechanism. In order to check this hypothesis, we have investigated the effects of PCP and of many other structural derivatives on the blastogenic response of murine or human T lymphocytes to mitogenic lectins. We find that, except ketamine, all the drugs we tested block an early event of T lymphocyte activation and prevent their further proliferation; conversely, when added later after the mitogen, they do not affect primed lymphocytes; in the same way they do not inhibit the IL-2 dependent proliferation of the cytotoxic T cell line. The inhibitory action of the drugs can be reversed by extensive washings of the cells. At concentrations preventing lymphocyte blastogenesis, PCP and its derivatives do not inhibit interleukin-1 (IL-1) production from LPS-stimulated macrophages, which suggests that these cells are not the target of the drugs. Conversely, they lower interleukin-2 synthesis from activated T helper cells. The inhibition of IL-2 production paralleled that of lymphocyte proliferation. The negative action of all the drugs appears to be related to the inhibition of the rise of $[Ca^{++}]_i$ (free cytosolic calcium concentration) observed soon after the T receptor triggering and which is an essential message for IL-2 production. Lymphocyte membrane depolarization induced by the drugs could explain the blockade of the lectin-induced $[Ca^{++}]_i$ changes. The study of the structure-activity relationship shows that the PCP analogs which possess a quasi-rigid conformational structure express an inhibitory capacity of the T lymphocyte proliferation higher than that of PCP (200 times for some products). Since these compounds poorly interact with the CNS tissues and have few comportmental effects, we suggest that PCP exerts its negative action in lymphocytes on biochemical entities different from its receptor(s) in the CNS; this could explain that ketamine has no action on lymphocyte mitogenesis.

EFFECTS OF DRUGS ON PHENCYCLIDINE STIMULATED LOCOMOTION AND ATAXIA IN MICE. Downs, D. A., J. N. Wiley and R. J. Labay. Department of Pharmacology, Warner-Lambert/Parke-Davis, Ann Arbor, MI 48105.

Phencyclidine caused dose-related increases in explora-

tory locomotor activity in mice at doses of 0.1 through 3.0 mg/kg IP, whereas higher doses caused less stimulation (10.0 mg/kg) or inhibited (30.0 mg/kg) exploratory locomotion. Numerous drugs of various classes were examined for their ability to selectively inhibit exploratory locomotion after a maximally stimulating dose (3.0 mg/kg) of PCP. None of the drugs which we examined consistently or selectively inhibited PCP-stimulated locomotor activity. That is, all drugs which reduced PCP-stimulated locomotion caused comparable percentage reductions of normal exploratory locomotion. However, because PCP alone had a biphasic dose-response, it was difficult to determine whether drugs which appeared to reduce PCP-stimulation had shifted the PCP dose-response curve to the left or to the right or simply reduced the maximum. Thus, when a drug appeared to reduce the locomotor stimulant effect of 3.0 mg/kg of PCP, it was always necessary to examine additional doses of PCP in the presence and absence of the second drug. Doses of PCP that maximally stimulated locomotor activity (e.g., 3.0 to 4.0 mg/kg IP) also caused mice to fall from a wire mesh platform when inverted 180 degrees, an effect which can be described as stimulated ataxia. We judged this procedure to be superior to locomotor activity measurement for examining anti-PCP effects, since the dose-response to PCP itself was monophasic. Again, none of the drugs which we tested appeared to antagonize this effect of PCP in mice. We conclude that none of the following drugs selectively block PCP-stimulated locomotion or ataxia in mice:

4-aminopyridine	diprenorphine	NMDA
d-amphetamine	haloperidol	phentolamine
apomorphine	ketamine	physostigmine
atropine	1-PIA	piracetam
baclofen	mephenesin	prazosin
bicuculline	meprobamate	propranolol
bromocriptine	metaphit	pyrilamine
chlorpromazine	methadone	quipazine
cimetidine	methysergide	reserpine
clonidine	morphine	rimcazole
clozapine	muscimol	THA
cyproheptadine	naloxone	yohimbine
diazepam	NECA	

INTRAVENOUS ANESTHETIC ACTIVITY OF BICYCLIC KETALS STRUCTURALLY RELATED TO KETAMINE AND ETOXADROL.

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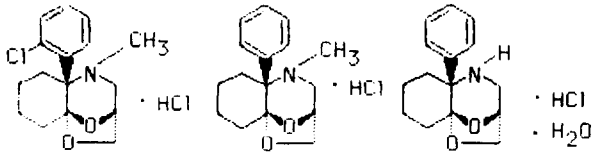
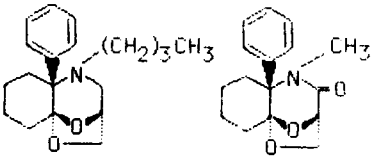
A limited series of bicyclic ketals bearing structural features common to the dissociative anesthetics ketamine HCl (K) and etoxadrol HCl (E) were prepared. The introduction of the ketal moiety of E into the K molecule provided the novel structural feature of this series.



A 46741 A 46519 A 47028



A 46682 A 46872

Screening for IV anesthetic activity was conducted in mice. Anesthetic ED50s for the reference compounds K, E and thiopental sodium (T) were 8.8, 15 and 20 mg/kg, respectively. The bicyclic ketal analog of K (A-46741) was inactive (ED50 > 50 mg/kg) but its deschloro derivative (A-46519) was anesthetic with an ED50 of 26 mg/kg, suggesting steric hindrance of the nitrogen. The importance of the secondary amine function present in both K and E was demonstrated with the N-desmethyl, deschloro ketal derivative A-47028 which had an ED50 of 8.5 mg/kg. Compounds A-46682 and A-46872 were inactive at a dose of 20 mg/kg. Acute LD50s of A-47028, K, E and T were 125, 82, 40 and 76 mg/kg, respectively, giving therapeutic indices of 14.7, 9.3, 2.7 and 3.8. The anesthetic activity of this bicyclic ketal series was confirmed in the rhesus monkey. Male rhesus monkeys, weighing 2.8–3.3 kg, were administered the test compounds by injection into the saphenous vein. The drugs were prepared as solutions in sterile water and were injected at a rate of 1 ml/min. Evaluation of anesthesia and related signs and symptoms was accomplished by the use of a twenty point check list adapted from Chen and Weston (Anesthesia and Analgesia **39:** 132, 1960). The monkeys were observed for onset and duration of and recovery from the anesthetic effects of K or the test drugs. Intravenous administration of two of the test compounds or K produced an immediate onset of anesthesia in rhesus monkeys. A-47028, at intravenous doses of 10.95 and 21.9 mg/kg, also produced anesthesia which was similar to that produced by K in equimolar doses of 10 and 20 mg/kg. The recovery times for A-47028 treated animals were longer than those of the K treated animals. A-46519, at intravenous doses of 10.8 and 21.6 mg/kg, produced anesthesia which was about equal to K (10 and 20 mg/kg) in duration and time to full recovery. A-46741 (12 and 24 mg/kg) produced no anesthesia when administered intravenously in rhesus monkeys.

PHARMACOLOGICAL STUDIES SUGGEST THAT *SIGMA* RECEPTORS LABELED *IN VIVO* WITH [^{3}H]-(+)-SKF10047 ARE PREDOMINATELY OF THE HIGH AFFINITY TYPE.

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The *sigma* receptor, so named because of the distinct pharmacological profile produced by its prototypic agonist SKF-10047 (N-allylnormetazocine), is believed to mediate mania and other psychotomimetic effects in man. While this *sigma* receptor has received extensive characterization *in vitro*, little information is available on the nature of the *sigma* site *in vivo*. It is possible to label dopaminergic, opiate, cholinergic, serotonergic and benzodiazepine receptors *in vivo* after IV administration of appropriately labeled ligands. In the present study, we describe the *in vivo* labeling of