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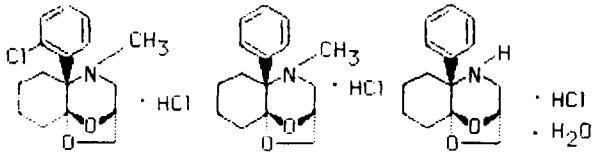
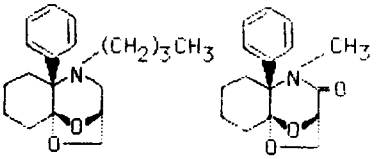
A limited series of bicyclic ketals bearing structural features common to the dissociative anesthetics ketamine HCl (K) and etoxadrol HCl (E) were prepared. The introduction of the ketal moiety of E into the K molecule provided the novel structural feature of this series.



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

sigma receptors in mouse brain using (+)-[^{3}H]-SKF10047 as a ligand, and have attempted to compare the relative potencies of various drugs on *sigma* sites *in vivo* and *in vitro*. Mice were injected with 5 μCi of (+)-[^{3}H]-SKF10047 into the tail vein. After various time intervals, the mice were decapitated, their brains were rapidly removed, weighed, homogenized and total and particulate (specific and nonspecific) bound radioactivity were determined (detailed methodology will be presented). Specifically bound (+)-[^{3}H]-SKF10047 in the particulate fraction was defined as the difference in total radioactivity in the particulate fraction obtained from vehicle injected mice minus the radioactivity in the particulate fraction from Haldol (2 mg/kg IP) injected mice. Specifically bound (+)-[^{3}H]-SKF10047 in the particulate fraction reached peak levels 30 min after IV injection, declined rapidly over the next 120 min, and constituted 90–95% of the total particulate radioactivity. Labeling of the *sigma* sites could be blocked *in vivo* by injecting mice IP with the drug 30 min before the IV injection of the [^{3}H]-ligand. Under these conditions, the site in brain labeled by [^{3}H]-(+)-SKF-10047 had the following characteristics: (1) naloxone insensitive; (2) stereoselective towards (+)-enantiomers of certain benzomorphan opiates like N-allylnormetazocine; (3) high affinity for haloperidol, (+)-3-PPP, cyclazocine, pentazocine and (+)-SKF-10047, and; (4) weak affinity for NMDA, (−)-3-PPP, PCP, and m-NH_2-PCP. This pharmacological profile would suggest that we are preferentially labeling the high affinity *sigma* site rather than the low affinity *sigma*/PCP site *in vivo* with [^{3}H]-(+)-SKF-10047. Attempts to label the low affinity *sigma*/PCP site *in vivo* with ^{3}H-TCP have failed. Thus, this *in vivo* binding assay should be a useful new technique for studying the effect of drugs on high affinity sites in the intact animal and for correlating these data with behavioral responses elicited over the same dose ranges.

INTERACTIONS OF PCP AND DERIVATIVES WITH THE BINDING OF ^{3}H 5-HT AND ^{3}H-MINAPRINE IN RAT BRAIN. Fillion, G., J. M. Sani, F. Christophe de Lamotte. Unite de Pharmacologie Neuroimmunoendocrinienne, Institut Pasteur, Paris, France.

PCP has been previously described to interact with the serotonergic system at the uptake sites (Smith, 1977) and at the 5-HT_2 receptors (Nabeshima, 1984). The present study was performed to examine the interactions of PCP (GK_1), TCP (GK_0) and GK_{13} at the high affinity 5-HT sites. One class of sites (5-HT_1) corresponds to a serotonergic receptor able to recognize ^{3}H 5-HT with a high affinity (K_D=3 nM) through distinct subclasses (5-$HT_{1A'B'C'D}$); one of them is likely related to a high apparent affinity adenylate cyclase activation. The effects of PCP and derivatives are not constantly observed at concentrations close to 10^{-5} M; they might induce a modest increase (+16%) (GK_{13}) or decrease (20–40%) (GK_0, GK_1) of the 5-HT_1 binding. The effects of these substances are quite constant and significant on a second population of ^{3}H 5-HT binding sites having an intermediate affinity (K_D=10 nM). GK_0, GK_1 and GK_{13} decrease the binding of ^{3}H 5-HT with IC 50's close to 10^{-5} M. These results show that PCP and derivatives interact with ^{3}H 5-HT binding; the interactions appear as non competitive phenomena. The effects of these substances also have been examined on the binding of an antidepressant, ^{3}H-minaprine (^{3}H-MIN) to hippocampal membranes which likely interacts with the ^{3}H 5-HT binding. An enhancement of the ^{3}H-MIN binding has been observed which corresponded to an increase in the Bmax accompanied by a change in Hill coefficient. These results suggest that PCP and derivatives not only may interact with the serotonergic function through complex molecular mechanisms affecting the binding of the amine to its specific sites, but indicate that they could also modify the binding of antidepressants to their specific sites. At the present time it is not known whether these molecular activities of PCP and derivatives correspond to clinical changes.

PHARMACOLOGICAL SPECIFICITY OF THE ELECTROPHYSIOLOGICAL EFFECTS OF PCP AND BENZOMORPHANS ON CEREBELLAR PURKINJE NEURONS. Freedman, R., Y. Wang, M. Kim, E. Moore, B. Hoffer and M. R. Palmer. Departments of Pharmacology and Psychiatry, University of Colorado Health Sciences Center, Denver, CO 80262.

Noradrenergic neurons have a well characterized input to cerebellar Purkinje neurons which we have previously found to be sensitive to presynaptic actions of phencyclidine (PCP). In our previous studies, we found that PCP causes depressions of the firing rates of single Purkinje neurons by potentiating synaptically released norepinephrine (NE). This effect appears to be caused by a blockade of synaptic reuptake of NE as well as, perhaps, by the potentiation of ongoing NE release. More recently, we have characterized the pharmacological specificity of PCP actions in cerebellum using the putative PCP receptor blocker, metaphit. Metaphit irreversibly blocked the electrophysiologically recorded depressions of Purkinje neurons caused by local applications of PCP, but not those caused by the inhibitory neurotransmitters, NE and GABA. Metaphit also blocked the depressions caused by local applications of the specific PCP-receptor agonist, dexoxadrol, but not the effects of its stereoisomer, levoxadrol. Furthermore, noncompetitive antagonists of *mu* and *delta* opiate receptors, BIT and FIT respectively, which contain an isothiocyanate moiety identical to that of metaphit, did not antagonize the effects of either dexoxadrol or PCP. We have also found that cyclazocine, a psychoactive benzomorphan, causes both metaphit-sensitive and metaphit-insensitive responses in cerebellum. The metaphit-insensitive responses were reversed by high doses of naloxone, suggesting a possible *kappa* opiate mechanism in addition to a metaphit-sensitive PCP mechanism. Both the (+) and (−) enantiomers of the benzomorphan *sigma* receptor agonist, SKF 10,047, caused depressions of Purkinje neurons which could be antagonized by metaphit. Unexpectedly, however, high doses of naloxone also partially antagonized the effects of these compounds. The naloxone applications also reversibly blocked the effects of concomitantly applied U-50, 488H, a highly selective *kappa* agonist, suggesting at least a small contribution of *kappa* mechanisms to the responses caused by both SKF 10,047 enantiomers.

PHENCYCLIDINE-INDUCED CHANGES IN A_{10} DOPAMINE NEURONAL ACTIVITY AND LOCOMOTOR BEHAVIOR IN RATS CHRONICALLY TREATED WITH PCP. French, E. D. Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD 21228.

A number of *in vivo* and *in vitro* studies have examined a