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

variety of effects produced by acute phencyclidine (PCP) administration. However the cellular changes resulting from long-term exposure to PCP are less well understood and in some cases conflicting. Chronic PCP abuse in humans has been associated with severe and occasionally permanent personality changes resembling psychotic symptomatology. Midbrain ventral tegmental (VTA) dopamine neurons have been suggested as a pivotal substrate involved in schizophrenia. Since this same VTA system has been shown to mediate prominent PCP-induced behaviors in rats the present study was designed to determine the effects of PCP on A_{10} neuronal activity and locomotor activity in animals receiving long-term (30 days) daily injections of PCP. Standard extracellular recording procedures were used in anesthetized rats. Only neurons with biphasic or triphasic action potentials <2 msec and firing rates of 1–9 spikes/sec and histologically localized within the VTA were included in the analysis. Changes in activity were quantitated after each incremental IV injection of PCP and dose-response curves constructed. Locomotor activity was measured (photocell equipped cages) for 2 hr after the 1st and 30th injection of PCP (5 mg/kg). The response of presumptive A_{10} cells to PCP was assessed in 20 chronic vehicle and 20 chronic PCP-treated rats. Analysis of the dose-response data revealed a non-significant 37% difference between treatment groups. Basal firing rates were virtually identical in both groups, as was the unique characteristic response pattern of A_{10} cells of PCP, namely excitation/inhibition. Thirty-one of the 40 neurons included for analysis also were inhibited by apomorphine: an effect reversed by haloperidol. Locomotor activity and time-course of effect were nearly identical after the 1st (1097 counts/2 hr) and 30th (1106/2 hr) injection of PCP. These findings suggest that long-term exposure to PCP does not readily induce a state of tolerance in a population of neurons subserving a prominent PCP-associated behavior. Since this analogous group of midbrain cells has been historically linked to the etiology of schizophrenia, our findings may provide some insights into the possible substrates underlying the development of psychotic-like symptomatology that has been reported to develop in some individuals who repeatedly abuse PCP for prolonged periods of time. (Supported by USPHS grant DA 03876.)

COMPARATIVE EFFECTS OF PHENCYCLIDINE, KETAMINE AND MK-801 ON THE RAT ELECTROENCEPHALOGRAM (EEG). French, J., P. Ho and E. F. Domino. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0626.

Characteristic EEG effects from the neocortex and hippocampus were compared following phencyclidine (PCP), ketamine and MK-801. A total of 6 adult, male, Sprague-Dawley rats were chronically implanted with bipolar EEG and temporalis muscle electrodes. Each rat was placed in a Plexiglas chamber 30 cm in diameter by 29 cm deep and recordings were obtained on polygraph paper and FM magnetic tape. Additionally, gross body movements and EEG data were collected simultaneously on a video/analog cassette recorder. Cumulative doses of PCP (3.2, 10, 32 and 56 mg/kg), ketamine (10, 32, 100 and 180 mg/kg) and MK-801 (1, 3.2, 10 and 32 mg/kg) as base content, were administered IP every 15 min. Rats were used every 2–4 days to allow for drug elimination. A Latin Square design was used such that the order of drug presentation was random for each rat. Maximal doses were based on 75–80% of the estimated LD50 for each compound. Many behavioral and EEG features common to all three compounds were observed. Small doses produced side to side head movements and stereotyped circling behavior which were accompanied on the EEG by large amplitude irregular activity from the hippocampus and large slow waves (1–3 Hz) from the neocortex. The amplitude of the electromyogram (EMG) also was increased. After intermediate doses of these agents, most rats were unable to support themselves. The amplitude and incidence of large amplitude irregular activity in the hippocampus and slow wave in the cortex increased. After even larger doses, episodic sharp waves began to appear from both EEG leads and the animals were typically unable to right themselves. For PCP, this EEG sharp wave activity was correlated with the EMG. The largest dose of each compound produced an increase in the frequency and occurrence of all aberrant wave forms in both leads. However, only PCP produced pronounced but brief EEG and EMG seizure activities and only ketamine produced effective, general anesthesia. After 1 hr post dosing, sharp activity decreased while the incidence of background 15–20 Hz activity increased in both leads. After 7 hr gross behavior and EEG partially recovered and by 24 hr, returned to baseline levels. It is concluded that while all three agents have similar EEG and gross behavioral features, depending on dose, there are distinct differences which make a simple classification difficult. (Supported in part by NIDA grant DA 1531.)

PHENCYCLIDINE-INDUCED IMMUNODEPRESSION. Fudenberg, H. H. Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina, Charleston, SC 29425.

Phencyclidine (PCP or angel dust) and some of its derivatives are psychotomimetic drugs that have been used in general anesthesia for some time. PCP blocks potassium ion channels in brain tissue, and there is a specific PCP binding to lymphocytes. Heat polymerized PCP binds to potassium ion channels in T-cells and prevents production of IL-2 and other lymphokines. PCP depressed immunocyte function *in vitro*, both humoral response (measured by IgM and IgG production) and cellular immune response as measured by incorporation of ^{3}H-thymidine of CD_4+ and CD_8+ T-cells and B-cells, by ^{3}H-deoxyglucose uptake *in vitro* and IL-1 production by monocytes. All these were depressed when immunocytes were treated with PCP before biological assay. This finding has implications for PCP abuse, especially in the chronic organic brain syndromes mimicking schizophrenia that develop in a small percent of PCP users independent of frequency or duration of PCP use. In other studies we used peripheral blood lymphocytes to study the effects of PCP on various receptors. We observed similar effects in binding to *sigma* receptors (inhibition of binding and reversibility of binding) in receptors of both human peripheral blood immune cell hydrid clone. The results are compatible with the hypothesis that some cases of schizophrenia are immunologically mediated, perhaps due to antibodies to the *sigma* receptor. Alternatively, immunologic deficiency might hinder elimination of neurotropic viruses which in genetically predisposed individuals bind to and block the *sigma* receptor. Functional deficiency of the brain cell equivalent of lympho-