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-

cyte suppressor T-cells by one or another immunologic mechanisms or an excess of T-helper cells might also cause schizophrenia by causing an excess of normal brain "B-cell equivalent cell" output response to sensory input.

PCP RECEPTORS IN HUMAN IMMUNE CELLS: PCP-INDUCED IMMUNOSUPPRESSION AND PREVENTION THEREOF BY ALPHA-1 ACID GLYCOPROTEINS. RELEVANCE TO PCP-INDUCED CHRONIC ORGANIC BRAIN SYNDROME. Fudenberg, H. H. and V. K. Singh. Department of 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 we have shown specific PCP binding to lymphocytes from human peripheral blood. Heat polymerized PCP binds to potassium ion channels in T-lymphocytes and prevents production of IL-2 and other lymphokines. PCP depresses 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 CD4d and CD8+ T-cells and B-cells, by ^{3}H-deoxyglucose uptake *in vitro*, and IL-1 production by monocytes. All these were depressed when normal 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 percentage of PCP users independent of frequency or duration of PCP use. In other studies, receptor binding of ^{3}H-PCP to membranes of rat lymphoid tissues were considerably higher than in other tissues and were 4-fold higher in thymocyte membrane than in spleen or brain cells. Indirect evidence for the presence of a specific receptor for PCP in normal human periphery blood immune cells was provided by positive-staining of lymphocytes (about 60%), with fluorescein-labelled anti-PCP; presumably the epitope of PCP is very similar to the endogenous ligand "alpha endopsychosin" (D. Maggio *et al.*, these proceedings). As noted above, PCP causes depression of several immune functions *in vitro;* at least one such function, namely lymphocyte DNA synthesis, can be restored to normal levels by Om, a major alpha-1 globulin of normal plasma which we have shown to be an immunoregulatory protein (Singh and Fudenberg, 1987). Since Om and PCP are present (based upon the specific binding of anti-Om and anti-PCP) on immunocyte membranes and both interact with each other, we suggest that Om may compete with PCP in binding to potassium ion channels that are present in the membranes of both nerve and immune cells that can be blocked selectively with PCP (Vincent *et al.*, 1983; Blaustein and Ickowicz, 1983). In the PCP-induced form of chronic organic brain disease, PCP might block these potassium ion channels resulting in impaired neurotransmission or binds to surface-membrane-associated Om, which may otherwise be freely available for the performance of normal cellular functions. Alternatively, autoantibodies to PCP-receptor, much like autoantibodies to insulin receptor in insulin-dependent diabetes or autoantibodies to nicotinic acetylcholine receptor in myasthenia gravis, may be important in the pathophysiology of one form of chronic PCP-schizophrenia-like form of psychosis. Autoantibodies to "endopsychosin" might be an additional mechanism relevant to the induction of PCP-psychoses. Alternatively, the immunologic deficiency induced by PCP might predispose to infection of neurotropic viruses which in genetically predisposed individuals might bind to and block the endopsychosin receptor. Functional deficiency of the brain cell equivalent of lymphocyte suppressor T cells by one or another immunologic mechanisms or an excess of the brain equivalent to contrasupport cells. T cells might also cause schizophrenia by causing an excess of normal brain "B-cell equivalent cell" response to sensory input.

ANALYSIS OF PHENCYCLIDINE (PCP) AND OTHER STRUCTURALLY RELATED COMPOUNDS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY (GC-MS). Gole, D. J., J. L. Pirat and E. F. Domino. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0626.

Over the past two decades a number of research laboratories have directed their efforts to find a PCP antagonist, to discover more specific PCP-like drugs, as well as to study PCP biotransformation. These efforts have led to the synthesis of a large number of structurally related agents. We have developed an analytic method to identify over 100 of these compounds by GC-MS techniques. A HP 5890 gas chromatograph equipped with a mass selective detector with a direct interface was used for sample analysis. A high performance fused-silica capillary column with cross-linked methyl silicone bonded phase (12 m length × 0.2 mm i.d. × 0.33 μM thickness) was found suitable for separation of these compounds. Each sample was injected into the GC using a splitless mode with a HP 7363A autosampler. The temperature of the splitless injection port and the detector were 250°C and 195°C, respectively. Thermal degradation was held to a minimum by gradually increasing column temperature. The oven temperature was initially at 100°C for 0.5 min, and then was increased linearly at a rate of 10°C/min and finally held at 250°C for 6 min to purge the column. The column head pressure of the carrier gas helium was 5 psi and the split vent was set at flow rate of 2 ml/min. Data acquisition was done on a HP 9000 series computer. Analytic amounts of the various compounds were obtained from one of the following sources: National Institute of Drug Abuse, Rockville, MD 20857, Kamenka, J. M., CNRS LP 8402-INSERM U 249, Ecole Nationale Superieure de Chimie, 8, rue de l'Ecole Normale 34075 Montpellier, France; Kalir, A., Institute of Occupational Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978 Israel and Warner-Lambert/Parke-Davis, Ann Arbor, MI 48105. The mass spectral and gas chromatographic data of these compounds are illustrated. The mass fragmentation pattern of these compounds is discussed and presented according to the structural modifications of the aryl, cyclohexyl or piperidine rings of the PCP molecule. (Supported in part by NIDA grant DA 1531.)

NEW ASPECTS OF PHENCYCLIDINE (PCP) METABOLISM. Gole, D. J., J. L. Pirat and E. F. Domino. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0626.

A high performance capillary column gas chro-