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.

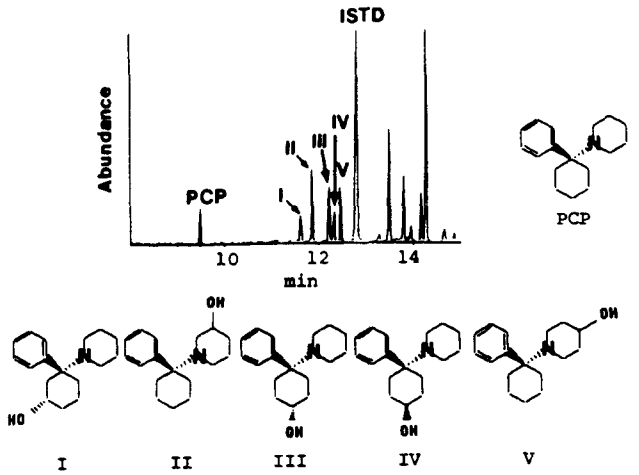
ANALYSIS OF PHENCYCLIDINE (PCP) AND OTHER STRUCTURALLY RELATED COMPOUNDS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY (GC-MS). Gole, D. J., J. L. Pirat and E. F. Domino. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0626.

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-

matography-mass spectrometry (GC-MS) procedure was developed to identify PCP, its major metabolites, other PCP analogs and derivatives. The method described is able to separate *m*-OH, *p*-OH, 3-OH pip (II), 4-OH pip PCP (V) and the stereoisomers of 2-OH cyclo, 3-OH cyclo and 4-OH cyclo PCP (III,IV). A sensitive and specific quantitative method was also developed to measure some of these monohydroxy substituted metabolites of PCP from biological samples. The method is based on a two step extraction of PCP related basic metabolites in an organic solvent followed by GC separation and mass selective detection of the extract derivatized with N,O *bis* (trimethylsilyl) trifluoroacetamide. The detection limit of the method was about 5 pmol per injection with a linear standard curve to 3 nmol. The assay was used for the quantitation of monohydroxy metabolites in the urine of PCP-dosed mice and rats. A typical chromatogram of the separation of various PCP metabolites in mice urine is shown below with the labelled peaks identified and remaining peaks unidentified. The 3-CH_2OH pip PCP served as the internal standard (ISTD). The *in vitro* biotransformation of PCP by mouse and rat liver microsomes was also studied. The presence of a recently identified metabolite, *trans* 3-OH cyclo PCP (I), was confirmed. A new metabolite, 3-OH pip PCP (II) was identified and quantitated in the urine and liver microsomal preparations. (Supported in part by NIDA grant DA 1531.)



BINDING STUDIES IDENTIFY TWO CLASSES OF PHENCYCLIDINE (PCP) RECEPTORS IN RAT BRAIN. Haring, R., Y. Kloog and M. Sokolovsky. Laboratory of Neurobiochemistry, Department of Biochemistry, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel.

Binding experiments were employed in order to differentiate between PCP-receptor sites in rat brain. Two classes of PCP receptors were characterized and localized: one binds [^{3}H]-N-[1-(2-thienyl-cyclohexyl]piperidine ([^{3}H]TCP) with high affinity (K_d=10–15 nM) and the other binds the ligand with a relatively low-affinity (K_d=80–100 nM). The neuroleptic drug haloperidol did not block binding either to the high- or to the low-affinity [^{3}H]TCP sites whereas Ca^{2+} inhibited binding to both. Monovalent ions (K^+ or Na^+) selectively inhibited binding of [^{3}H]TCP or of [^{3}H]PCP to the high affinity sites, via an allosteric mechanism, resulting in the conversion of the high affinity sites to a lower affinity state, which is indistinguishable from the preexisting low affinity site. The two classes of [^{3}H]TCP binding sites have different patterns of distribution. Forebrain regions are characterized by high-affinity sites (hippocampus > frontal cortex > thalamus > olfactory bulb > hypothalamus) but some parts (e.g., hippocampus, hypothalamus) contain low-affinity sites as well. In the cerebellum and in the brainstem only low-affinity sites were detected. Binding sites for [^{3}H]PCP and for its photolabile analog [^{3}H]azido-PCP showed a regional distribution similar to that of the [^{3}H]TCP sites. The results are compatible with the existence of two classes of PCP receptors in the rat brain with a selective localization in the brain. (Supported in part by NIH Grant DABB IR01 DAO4168-01).

ETHYLKETOCYCLAZOCINE (EKC) ANTAGONIZES PHENCYCLIDINE (PCP)-INDUCED STEREOTYPED BEHAVIORS BY REDUCING MONOAMINE RELEASE. Hiramatsu, M., T. Nabeshima, H. Furukawa and T. Kameyama. Department of Chemical Pharmacology and *Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan.

Administration of PCP to rats induces a complex syndrome of behaviors such as hyperactivity, stereotypy and ataxia and it has been demonstrated that these behaviors are mediated via various neuronal systems. It has been suggested that the psychotomimetic effects of PCP are mediated by PCP/sigma receptors and that the psychotomimetic effects of opiates such as SKF 10,047 also reflect influences of the interaction of PCP/sigma receptors. Tam has suggested that the sedative effect of EKC can mask the observable sigma type behavioral responses. Our purpose in the present study was to investigate whether EKC can affect the PCP-induced stereotyped behaviors in rats. Male Wistar rats (200–300 g) were used. Stereotyped behaviors induced by PCP and SKF 10,047, dopamine-dependent behaviors induced by methamphetamine and apomorphine and serotonin-dependent behaviors induced by *p*-chloroamphetamine and 5-methoxy-N,N-di-methyltryptamine (5-MeODMT) were recorded by the method of Nabeshima *et al.*, Watanabe *et al. and Lee et al.* with some modification, respectively. PCP produced hyperactivity, ataxia and stereotyped behaviors consisting of sniffing, turning, head-weaving and backpedalling. PCP (7.5 mg/kg)-induced stereotyped behaviors were dose-dependently antagonized by EKC (0.25–4 mg/kg). Mr 2266 (2.5 mg/kg), a selective kappa opiate antagonist, antagonized the effect of EKC on PCP-induced stereotyped behaviors. Mr 2266 failed to affect PCP-induced stereotyped behaviors. It is known that PCP-induced stereotyped behaviors are mediated by the dopaminergic and serotonergic neuronal systems. Therefore, we investigated whether EKC affects the dopaminergic and/or serotonergic neuronal systems. EKC antagonized methamphetamine (a dopamine releaser)-induced dopamine-dependent behaviors and *p*-chloroamphetamine (a serotonin releaser)-induced stereotypy, but not apomorphine (a dopamine receptor agonist)-induced dopamine-dependent behaviors and 5-MeODMT (a serotonin receptor agonist)-induced serotonin-dependent behaviors (hind-limb abduction, forepaw treading and Straub tail reaction). These results suggest that EKC, a presumed kappa opioid receptor agonist, antagonized the PCP-induced stereotypy