branes, whereas the effects of (+)-[$^3$H]-SKF10,047 on isolated guinea-pig ileum preparation have been described by Su *et al.* (*Life Sci* **28:** 2519, 1981), and Kromer *et al.* (*Naunyn Schmiedebergs Arch Pharmacol* **321:** 218, 1982). The present work was thus carried out in order to characterize binding sites for (+)-[$^3$H]-SKF10,047 in guinea-pig myenteric plexus membrane preparations. A saturable specific binding was found when (+)-[$^3$H]-SKF10,047 concentrations were increased from 1 to 50 nM. The equilibrium was reached in about 30 min. Dissociation was complete in 20–30 min. Specific binding was linear with protein concentration up to 1.2 mg/ml. In the range of concentrations explored, a binding site with $K_D$ of 42.2±2.2 nM and a Bmax of 3.19±0.34 pmole/g tissue was determined from Scatchard plot. Morphine and naloxone were inactive up to $10^{-4}$ M. Among the other compounds tested, haloperidol, imipramine, ketocyclazocine and propranolol were the most potent to displace (+)-[$^3$H]-SKF10,047 from guinea-pig myenteric plexus membranes. In contrast PCP was much less active ($IC_{50}$=2.5 $\mu$M) a result which is at variance with those reported with guinea-pig whole brain membranes ($IC_{50}$=65 nM). These experiments suggest that *sigma* receptors are present in the guinea-pig myenteric plexus and put forward a putative physiologic role of *sigma* receptors at the gastrointestinal tract level.

PUTATIVE ROLE OF PCP-TCP RECEPTORS IN THE EFFECTS OF KINDLING. *Rondouin, G., I. Chaudieu, J. M. Kamenka and R. Chicheportiche. CNRS LP 8402-INSERM U 249, Ecole Nationale Superieure de Chimie, 8 rue de l'Ecole Normale, 34075 Montpellier Cedex, France; *Laboratoire de Medecine Experimentale, Bd Henri IV, 34060 Montpellier Cedex, France.

Phencyclidine (PCP) has been reported to delay the rate of kindling in rats. This drug and other *sigma* compounds were also reported to block long term potentiation, which mechanisms are partially related to those of the kindling effect. This study investigated the effects of thienylcyclidine (TCP) and some TCP derivatives in kindled rats. TCP and GK103 neither significantly reduced the duration of afterdischarges in kindled rats nor had a clear-cut anticonvulsant effect. The effects on behavioral stages of kindling were rather related to the ataxic effect of these two drugs. Conversely, GK115 blocked kindled seizures without producing an ataxic side-effect. Kindling also induced modifications in the binding parameters of $^3$H-TCP, both in the cortex and in the cerebellum. These results will be discussed according to the multiple binding sites of these compounds.

THE RAT BRAIN PHENCYCLIDINE (PCP) RECEPTOR: A PUTATIVE K CHANNEL. Sorensen, R. G. and M. P. Blaustein. Department of Physiology, University of Maryland School of Medicine, Baltimore, MD 21201.

$^{86}$Rb efflux studies on rat brain synaptosomes (Bartschat and Blaustein, *PNAS* **83:** 189, 1986) show that PCP selectively blocks a voltage-dependent, non-inactivating K channel. This suggests that the brain PCP receptor may be associated with this K channel. The present study provides PCP receptor binding data which support this proposal. Aminopyridines (AP) and tetraalkylammonium ions (TAA), compounds which block voltage-dependent K channels, compete with [$^3$H]PCP for binding to rat brain synaptic membanes. Their orders of potency are: for the APs, 4-AP=3,4-diAP > 2-AP >> 3-AP, and for the TAAs, tetrabutylammonium (TBA) > tetraethylammonium > tetramethylammonium. These sequences agree with those reported for the ability of the APs and TAAs to block K channels or to increase neurotransmitter release (an effect which results from the block of K channels). The nature of the interactions of the APs and TAAs at the PCP receptor were further studied. Reciprocal and Schild plot analyses indicate that TBA is a competitive inhibitor at the PCP receptor. 4-AP has a more complex interaction, probably an allosteric inhibition: the results suggest that 2 mol of 4-AP are required to displace 1 mol of PCP at the receptor. These data show that K channel blockers interact directly with the brain PCP receptor. Additional data also implicate the PCP receptor as a K channel. One, the order of potency of PCP and several analogs for block of the synaptosome K channel, [TCP (thienyl analog) > m-amino-PCP > PCP > m-nitro-PCP], is the same as the order of affinities of these compounds for binding to the PCP receptor and for producing behavioral deficits. Two, the stereospecific binding of the "sigma" opiate, N-allylnormetazocine (NANM), [(+NANM > (−)NANM] and the dioxolane, dioxadrol, [dexoxadrol >> levoxadrol], to the PCP receptor are similar to those determined for their block of the synaptosome K channel. Reciprocal and Schild plot analyses demonstrate that (+)NANM and dexoxadrol are competitive inhibitors at the PCP receptor. Taken together, these results provide strong evidence that the brain PCP receptor is part of a K channel. We suggest that the behavioral deficit produced by PCP intoxication results from the ability of PCP to block this K channel. (Supported by NINCDS.)

STUDIES OF NEWER SYNTHETIC OPIOIDS: THE CARDIAC AND KINETIC EFFECTS IN CHILDREN AND PIGLETS. Stiller, R. L., P. J. Davis, D. R. Cook, M. D. Ingram, J. M. Perel and C. M. Roeber. Departments of Psychiatry, Anesthesiology and Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

Alfentanil (A), a structural analogue of fentanyl, is about

one-fourth as potent as fentanyl and has one-third the duration of action. Little information is available in infants and children. Since the newborn piglet's cardiovascular and pharmacokinetic systems closely resembles that of the human neonate, this study defined the acute hemodynamic-pharmacokinetics changes following moderate and high dose injection of A in neonatal piglets. *Methods.* Piglets aged 1–14 days, were anesthetized with thiopental 4 mg/kg and oxygen. Group I (N=6) received 85 μg/kg and Group II (N=6) received 200 μg/kg over 30 sec. Blood pressure was monitored by femoral artery catheter. Cardiac index (CI) is reported as thermodilution cardiac output divided by weight. Left ventricular contractility DPDT max, and left ventricular end diastolic pressure LVEDP were measured with a μmanometer-tipped catheter. The stroke volume index (SVI) and total peripheral resistance index (TPRI) were calculated. Measurements were obtained at 0 (T0 min baseline), 5 min (T5), and 15 min (T15) and 30 min (T30) postinjection. Changes in the cardiovascular measurements were assessed by a repeated measures analysis of variance (ANOVA) and a 2 way ANOVA. The pharmacokinetics were evaluated by model-independent methods. AUC, t 1/2 α, t 1/2 β, and Vdβ were calculated using standard formulas. *Results.* Except for an increase in LVEDP at 5 min, Group I showed marked hemodynamic stability; Group II, significantly increased MAP, LVEDP SVR and dP/dT. There was no change in CI (Tables 1 and 2). The pharmacokinetics could be described with a β elimination phase half-life of 37.3 min ±10.7 (mean±SD), Vdβ 1.1±0.58 L/kg and a clearance of 10.4±6.2 one/kg/min. *Discussion.* Our study demonstrates dose related cardiovascular changes with A, with A increasing contractility. The increase in contractility and preservation of CI is in marked contrast to the cardiovascular effects of fentanyl in neonatal piglets. Thus it appears that A may offer more hemodynamic stability than fentanyl. (Supported in part by CRC MH 30915.)

ELECTROPHYSIOLOGICAL ACTIONS OF SIGMA LIGANDS IN THE *IN VITRO* HIPPOCAMPUS. Swearengen, E., A. Malouf and C. Chavkin,* Department of Pharmacology, University of Washington, Seattle, WA 98195. (*presenting author).

Binding studies have demonstrated the existence of high and low affinity binding sites for +SKF-10047 in the hippocampus and other brain regions. While PCP is a psychotomimetic agent, presumably acting through the low affinity (sigma/PCP) receptor, the physiological or behavioral roles of the high affinity +SKF-10047 site are not clear. We compared the electrophysiological actions of the high affinity +SKF-10047 ligands +SKF-10047, 3-PPP, DTG and haloperidol to PCP in the CA1 region of the *in vitro* rat hippocampal slice. Bath application of 3-PPP, and +SKF-10047 at concentrations below 100 μM produced little or no change in spontaneous activity, membrane potential, input resistance, spike amplitude or width, AHP following a +1 nA/200 msec current pulse, threshold for orthodromically driven spikes or the amplitude or duration of the resulting IPSP. Application of DTG produced an artifactual shift in membrane potential and resistance during recordings with electrodes filled with 4 M potassium acetate. Recordings using 3 M KCl filled electrodes indicate that 100 μM DTG produced a reduction in spontaneous activity without any change in membrane potential or input resistance. Extracellular recordings of CA1 field potentials also demonstrate that bath application of PCP, +SKF-10047, DTG and 3-PPP at concentrations less than 100 μM had little or no effect on either sensitivity to stimulation of Schaffer collaterals or the amplitude of the orthodromically evoked primary population spike. Higher concentrations (1 mM) of these compounds produced a complete inhibition of the population spike which fully recovered 30–60 min following washout. Haloperidol (10 μM) was inactive and did not antagonize the DTG ef-

TABLE 1

| 85 μg/kg | MAP | HR | CI | LVEDP | dP/dT | TPRI | SVI |
|---|---|---|---|---|---|---|---|
| T0 Mean | 102 | 222 | 0.288 | 7.6 | 15,225 | 374 | 1.32 |
| SEM | ±1.7 | ±18.7 | ±0.028 | ±0.65 | ±732 | ±38 | ±0.13 |
| T5 | 112 | 200 | 0.284 | 6.8 | 15,006 | 411 | 1.47 |
| | ±4.5 | ±20.1 | ±0.024 | ±1.1 | ±878 | ±36 | ±0.17 |
| T15 | 112 | 227 | 0.283 | 6.0 | 15,445 | 410 | 1.31 |
| | ±4.5 | ±19.1 | ±0.021 | ±0.77 | ±732 | ±42 | ±0.17 |
| T30 | 109 | 142 | 0.253 | 5.0* | 16,323 | 445 | 1.07 |
| | ±4.4 | ±14.1 | ±0.016 | ±0.70 | ±688 | ±39 | ±0.121 |
| 100 μg/kg | | | | | | | |
| T0 | 119 | 209 | 0.276 | 7.4 | 15,957 | 433 | 1.33 |
| | ±4.3 | ±12.4 | ±0.009 | ±0.36 | ±549 | ±21 | ±0.065 |
| T5 | 135* | 176 | 0.280 | 9.2* | 16,689 | 487 | 1.60* |
| | ±3.9 | ±13.4 | ±0.013 | ±0.31 | ±1,171 | ±25 | ±0.078 |
| T15 | 129 | 197 | 0.281 | 6.6 | 17,275 | 462 | 1.46 |
| | ±2.8 | ±16.1 | ±0.011 | ±0.60 | ±1,024 | ±21 | ±0.110 |
| T30 | 127 | 210 | 0.260 | 6.8 | 17,568 | 493 | 1.23 |
| | ±3.5 | ±10.7 | ±0.013 | ±0.58 | ±629 | ±20 | ±0.046 |

*$p \leq 0.05$ from T0