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

fects. D-APV, a selective NMDA receptor antagonist, blocked opioid-induced afterpotentials in CA1 and dentate pyramidal cells. Since PCP has also been shown to inhibit NMDA receptor activation, albeit by different mechanisms, compounds acting at the low affinity sigma/PCP receptor should inhibit opioid-APV on afterpotentials. However unlike D-APV, PCP and 3-PPP (100 μM) antagonized the opioid-induced increase in sensitivity to afferent stimulation. 3-PPP was slightly less potent than D-APV in reducing afterpotential amplitude. The concentration required for these effects is over three orders of magnitude greater than the reported IC50 values of these compounds for the high affinity site. These results suggest that the physiological responses of both high and low affinity +SKF-10047 site sigma ligands are mediated through the low affinity sigma/PCP site in this system. (Supported by NS-23483 and GM0720. We thank Dr. Eckard Weber for the gift of ditolylguanidine (DTG).)

BIOCHEMICAL AND BEHAVIORAL ASPECTS OF SIGMA AND PHENCYCLIDINE RECEPTORS: SIMILARITIES AND DIFFERENCES.

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A binding site for the sigma agonist (+)-[^{3}H]SKF 10,047 which differs from the PCP binding site in brain regional distribution, drug selectivity, and in many aspects of neurochemistry has been identified. Both sigma (haloperidol-sensitive) and PCP binding sites exist in brain membranes of many animal species including mouse, rat, guinea pig, rabbit, and dog. Characterization of behaviors mediated by activation of these binding sites have been difficult because the prototypic sigma agonist (+)-SKF 10,047 interacts with both sigma and PCP binding sites. For example, PCP and sigma agonists produced (+)-SKF 10,047-like discriminative stimuli in rats trained to discriminate (+)-SKF 10,047. (+)3-PPP, a compound that binds selectively to the sigma receptor but does not bind to the PCP receptor, produced (+)-SKF 10,047-like discriminative stimuli. The data suggest that (+)-SKF 10,047 produces behavioral responses through the PCP receptor and sigma receptor.

BMY 14802: A POTENTIAL ANTIPSYCHOTIC AGENT THAT SELECTIVELY BINDS TO SIGMA RECEPTORS.

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Based on animal testing, BMY 14802 has been identified as a potential antipsychotic agent: it blocks the conditioned avoidance response in rats with a potency similar to that of clozapine, exhibits a clozapine-like profile in the Sidman avoidance test (Taylor *et al., Soc Neurosci Abstr* **11:** 114, 1985), inhibits apomorphine-induced stereotypy and climbing and amfonelic acid-induced hyperlocomotion (*ibid.;* Matthews *et al., JPET* **239:** 124, 1986). Unlike currently-marketed antipsychotic drugs, BMY 14802 does not induce catalepsy; in fact, it reverses the catalepsy induced by trifluoperazine. In addition, chronic drug administration does not result in changes in D-2 dopamine receptor number. Receptor binding studies have previously shown that BMY 14802 exhibits low affinity for D-2 dopamine binding sites *in vitro* and *in vivo* and is not metabolized to a more active form (Taylor *et al., op. cit.*). Moreover, BMY 14802 does not inhibit dopamine-stimulated adenylate cyclase in rat striatum (Yocca *et al., Trans Am Soc Neurochem* **17:** 244, 1986). Here we report that BMY 14802 does not bind to D-1 dopamine binding sites. It has been observed that some conventional antipsychotic drugs inhibit the binding of (+)-[^{3}H]SKF 10,047 (N-allylnormetazocine, NANM) *in vitro* to the "haloperidol-sensitive sigma" site in guinea pig brain, and it has been proposed that selective sigma antagonists, devoid of D-2 dopamine antagonist action, may represent a novel class of psychotherapeutic agents in the treatment of schizophrenia. The possibility that BMY 14802 might interact at the sigma site was investigated by studying the binding of (+)-[^{3}H]NANM according to the method of Tam and Cook (*PNAS* **81:** 5618, 1984). BMY 14802 inhibited radioligand binding with an IC_{50} value of 83 nM compared to 2.4 nM for haloperidol. Like other chiral inhibitors of binding at this site BMY 14802 displayed stereospecificity: The IC_{50} for the (+) form was 47 nM, and for the (−) form it was 450 nM. Saturation studies suggested that the inhibition of (+)-[^{3}H]NANM binding by (+)BMY 14802 displays low affinity for the site labeled by the phencyclidine analog, [^{3}H]TCP (IC_{50}>10,000 nM). These data suggest that BMY 14802 represents a potential antipsychotic agent with reduced liability for the side effects characteristic of currently-available drugs and may act by selectively, stereospecifically, and competitively binding to the sigma site. If clinically efficacious, BMY 14802 would represent a safer alternative to agents available for the treatment of schizophrenia.

SYNTHESIS OF A MOLECULAR HYBRID OF PHENCYCLIDINE AND DEXOXADROL.

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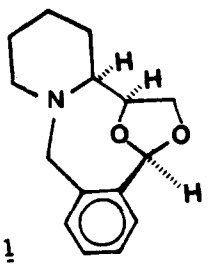
Phencyclidine and dexoxadrol have been shown to exhibit similar psychotropic qualities in vivo, and both bind with similar affinity to the PCP receptor. The compounds have two structural features in common, the piperidine and phenyl rings. While the rotational freedom of dexoxadrol allows for many possible conformations, we envisioned that the "PCP active" conformation (based on the absolute configuration of dexoxadrol obtained by x-ray crystallography) should be one in which the spatial positions of the piperidine ring and the phenyl were similar to those found in phencyclidine. To test this idea, we have synthesized a bridged dexoxadrol analog (1) which allows overlap between these pertinent structural features. The affinity of compound 1 to the PCP receptor has been determined.



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