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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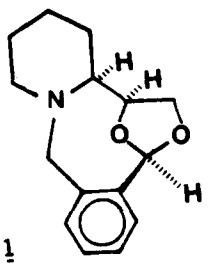
Phencyclidine and dexoxadrol have been shown to exhibit similar psychotropic qualities in vivo, and both bind with similar affinity to the PCP receptor. The compounds have two structural features in common, the piperidine and phenyl rings. While the rotational freedom of dexoxadrol allows for many possible 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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