Pharmacology Biochemistry & Behavior, Vol. 41, pp. 215–217. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/92 $5.00 + .00

RAPID COMMUNICATION

Sigma Ligand-Induced Emesis in the Pigeon

THOMAS J. HUDZIK

Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences
4301 W. Markham St., Slot 611, Little Rock, AR 72205

Received 2 July 1991

HUDZIK, T. J. *Sigma ligand-induced emesis in the pigeon.* PHARMACOL BIOCHEM BEHAV **41**(1) 215–217, 1992.—Pigeons were fed a fixed amount of grain-based feed and behavior was observed after administration of doses of ditolyguanidine (DTG), (+)-3-(3-hydroxyphenyl)-N-(1-propyl)-piperidine [(+)-3-PPP], dextromethorphan, haloperidol, (+)-N-allylnormetazocine (NANM), alpha-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine-butanol (BMY-14802) apomorphine, pentobarbital, propranolol, and MK-801. Of the drugs tested, DTG, dextromethorphan, and (+)-3-PPP each produced dose-related increases in the percentage of pigeons exhibiting an emetic response. The emetic response produced by DTG was antagonized by haloperidol and BMY-14802 but not by propranolol. These observations suggest that the emetic response in the pigeon may be mediated by sigma sites and is unlikely to be mediated by phencyclidine receptors.

Sigma site Emesis Ditolyguanidine BMY-14802 (+)-3-PPP Dextromethorphan N-Allylnormetazocine Haloperidol

OF Martin's classification of three opioid receptor subtypes (7) the sigma receptor has remained the most enigmatic. This site was thought to be the receptor for some benzomorphan opioids, such as N-allylnormetazocine (NANM) as well as phencyclidine, and linked to the psychotomimetic reactions of humans to these drugs (2). It has subsequently been shown that NANM and phencyclidine interact with at least two binding sites in the brain, one of which is termed the phencyclidine receptor (10,15), and is allosterically coupled to excitatory amino acid transmission (5). The physiology and pharmacology of the second site, the sigma site, are largely unknown.

Hypotheses regarding the function of the sigma site have ranged from suggestions that it is a metabolic enzyme (6) to a receptor complex with multiple, allosteric binding sites (1). A large group of drugs exist that have affinity for the sigma site, including DTG, (+)-3-PPP, BMY-14802, (+)-isomers of benzomorphan opioids such as NANM, phencyclidine, propranolol, the antitussive dextromethorphan, and neuroleptics such as haloperidol (11). Few of these drugs exhibit selectivity for the site, making determination of function difficult. The absence of any known physiological function for the sigma site has precluded the development of specific assays for determining the relative potencies and efficacies of sigma ligands. Furthermore, many of the effects of the benzomorphans, PCP, and dextromethorphan are likely accounted for by interaction with the PCP receptor. One recent attempt to characterize the potential involvement of the sigma site in the behavioral effects of drugs was conducted by Holtzman (3), who reported that in rats trained to discriminate DTG from saline, many drugs with affinity for the sigma site substituted for the DTG discriminative stimulus, but little correlation existed between receptor affinity and discriminative potency. It also has been suggested that sigma sites in the red nucleus may mediate certain types of motor responses (8,12), where a relationship appears to exist between binding affinity and potency to produce dystonia.

Emesis is a rare occurrence in pigeon and is not produced by drugs that typically cause emesis in other species, such as apomorphine. In previous experiments in this laboratory using food-reinforced behavior in the pigeon (in preparation), it was observed that DTG treatment produced a robust emetic response during operant sessions which was characterized by a forceful expulsion of feed. The goals of the present experiments were to determine which other drugs produce this effect and to assess whether the effect can be antagonized by other pharmacological agents.

METHOD

Subjects

Five male, white Carneaux pigeons, weighing 430–500 g at 80% of their free-feeding weights, were used. Animals were given free access to water, except during experimental sessions, and were fed 20 g of grain-based feed (Purina Pigeon Checkers) once per day. The colony room in which the animals were housed was illuminated from 6:30 a.m. to 6:30 p.m.

Animals were tested in their home cages between 10:30 a.m. and 12:00 p.m. Drug testing occurred each third day as follows. Water was removed from the cages, pigeons were fed a fixed amount (20.0 g) of Pigeon Checkers, and newspaper was placed below each hanging cage. Five min after feeding, a 1 ml/kg vol. injection of the following drugs was administered into the breast muscle: DTG (0.3–5.6 mg/kg), (+)-3-PPP (5.6, 10, and 30

mg/kg), haloperidol (0.1 and 1 mg/kg), (+)-N-allylnormetazocine (1, 3, and 10 mg/kg), dextromethorphan (3, 10, 17.8 and 30 mg/kg), apomorphine (0.1 and 1 mg/kg), pentobarbital (1 and 20 mg/kg). BMY-14802 (3, 10, and 30 mg/kg), propranolol (1 and 10 mg/kg) and MK-801 (0.1 and 0.3 mg/kg). If an emetic response was noted on test days, birds were fed an additional 15 g of feed 1 h after sessions ended.

Antagonism of the DTG response was examined by the administration of haloperidol (0.03–1 mg/kg), BMY-14802 (0.3–3 mg/kg) and propranolol (10 mg/kg). Haloperidol was administered 45 min prior to DTG; BMY-14802 and propranolol were administered 10 min prior to DTG.

Data Analysis

Subjects were scored as presenting a positive emetic response if regurgitated feed was observed on the newspaper under the cages 1 hour after injection with the test compound. ED_{50}s and 95% confidence limits were determined by the method of Litchfield and Wilcoxon (4). Animals were also observed for 2-min blocks every 15 min after injection, in order to note the emetic response as well as any other behavioral effects produced by the drugs.

Drugs

DTG, apomorphine HCl, haloperidol, propranolol HCl, and pentobarbital sodium were obtained from Sigma Chemical Co. (St. Louis, MO). (+)-3-PPP HCl was obtained from Research Biomedicals, Natick, MA and from Sigma Chemical. BMY-14802 was obtained from Bristol-Myers (Wallingford, CT). (+)-N-allylnormetazocine and dextromethorphan hydrobromide were obtained from the National Institutes of Drug Abuse (Rockville, MD). MK-801 oxalate was obtained from Merck (Rahway, NJ). All drugs were dissolved in sterile, distilled water with the exception of DTG, which was dissolved in a 1% (v/v) solution of lactic acid, after which the pH was titrated to 7.0 by addition of 1 N sodium hydroxide. Doses are expressed as the representative salts, with the exceptions of DTG and haloperidol, which are expressed as the free base.

RESULTS

Figure 1 shows the effects of DTG, dextromethorphan and (+)-3-PPP. Each of these drugs produced a dose-related emetic response in the pigeon within 45 min after injection, with ED_{50}s (95% confidence limits) of 2.75 (1.71–3.8), 8.51 (5.31–12) and 17.8 (14.8–21) mg/kg, respectively. There appeared to be a bimodal effect for dextromethorphan in that each of the 5 birds exhibited the emetic response after at least one dose, but some subjects did not exhibit the response at higher doses. Higher doses of (+)-3-PPP were not tested due to a limited supply of this drug.

(+)-NANM, BMY-14802, propranolol, apomorphine, and pentobarbital were inactive in producing the response when administered in doses up to those which produced marked ataxia or are known to produce response-rate decreasing effects upon operant behaviors in the pigeon, suggesting that behaviorally active doses of all compounds were used. Haloperidol was also ineffective, but it was not tested at doses that produced any grossly observable changes in behavior. Haloperidol pretreatment (0.1 mg/kg) did, however, result in a parallel, rightward shift in the DTG dose-effect curve (Fig. 2, left panel). Haloperidol and BMY-14802 also produced a dose-related antagonism of the effects of DTG (Fig. 2, right panel), with haloperidol being four-fold more potent than BMY-14802. Propranolol (10 mg/kg)

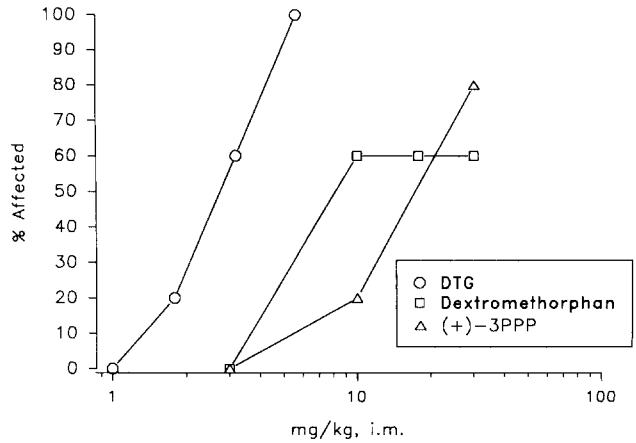

FIG. 1. Effects of doses of DTG, dextromethorphan, and (+)-3-PPP on the percentage of birds exhibiting an emetic response (n = 5).

in combination with DTG was lethal 40–50 min after injection in three of the five birds, and did not antagonize the emetic effect of DTG in any animal. The lethality was preceded for 10–20 min by a loss of righting, characterized by a progressive and marked decrease in muscle tone.

DISCUSSION

Each of the drugs tested that had activity in the present assay also has been shown to have affinity for the sigma site (13). However, haloperidol, BMY-14802, propranolol and (+)-NANM also have affinity for the sigma site, but did not produce the response, suggesting the possibility that sigma affinity may be a necessary but insufficient precondition to produce the effect or that DTG, (+)-3-PPP and dextromethorphan share some other, as yet unknown property. MK-801, which has a high degree of specificity for the PCP receptor (14) was also inactive at doses which produced marked ataxia, making it unlikely that interaction with PCP receptors underlies the effect.

The fact that both haloperidol and BMY-14802 were antagonists of the effects of DTG suggests that drugs may differ in their intrinsic efficacies at the sigma site, if indeed the effect is mediated by the sigma site. Although the antagonistic effects of haloperidol could possibly have been due to its interaction with postsynaptic D2 receptors, the fact that BMY-14802 was also an effective antagonist but does not interact with dopamine receptors (9) in addition to the fact that apomorphine was not an effective agonist suggests that dopamine receptors may not be directly involved in the antagonism. On the other hand, the rank potency order of the emetic drugs do not reflect their rank sigma site binding potencies. For example, the rank potencies to displace DTG from sigma sites is DTG > (+)-3-PPP >> dextromethorphan (15). However, the rank potencies of (+)-3-PPP and dextromethorphan were reversed in the present experiments. While this may suggest that the emetic response is not mediated by the sigma site, it is presently unclear to what extent pharmacokinetic factors as well as varying intrinsic efficacies may be involved in the in vivo potencies of these drugs. The beta blocker propranolol and the (+)-isomer of the prototypic sigma ligand, N-allylnormetazocine, were ineffective in producing the emetic response, and propranolol did not antagonize DTG's effects, suggesting that it is neither an agonist nor an antagonist. It remains to be determined if (+)-NANM is an antagonist of DTG's effects.

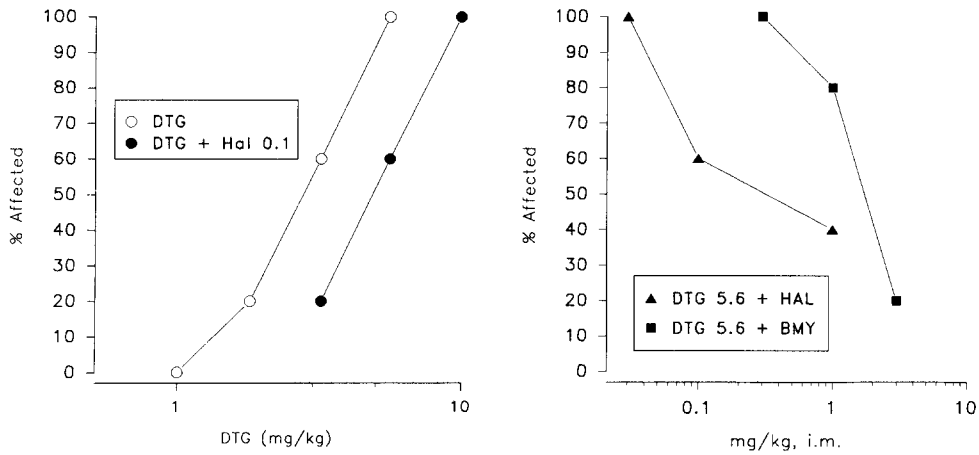

FIG. 2. Effects of doses of haloperidol (HAL) and BMY-14802 (BMY) on the emetic response to DTG (5.6 mg/kg).

The present experiments showed differences between (+)-NANM, which was inactive, and dextromethorphan, DTG and (+)-3-PPP. However, Holtzman reported that in rats trained to discriminate DTG from saline, (+)-NANM produced dose-related generalization from the DTG cue, suggesting that these compounds have similar, not different effects (3). Additionally, Holtzman was unable to antagonize the DTG discriminative stimulus by coadministration of haloperidol, although DTG did attenuate the effects of haloperidol on response latency. This suggests that the discriminative stimulus and motor effects of DTG may be mediated by different mechanisms. Moreover, Matsumoto et al. reported that DTG and haloperidol had similar motor effects in the rat and that (+)-3-PPP was inactive (7), which also contrasts with the present results. Species and procedural differences between the studies described and the present one are possible explanations for the disparity in results.

In summary, the present observations showed that a subclass of chemically disparate compounds with affinity for the sigma site can produce a novel response in the pigeon, emesis. Additionally, it was observed that the effect of DTG can be antagonized by haloperidol and BMY-14802, drugs that also have affinity for the sigma site. Although the relationship between the emetic response in the pigeon and behavioral effects in mammalian species remains to be clarified, this assay may provide a rapid, simple means of characterizing the pharmacology of sigma-like compounds.

ACKNOWLEDGEMENTS

The author wishes to gratefully acknowledge the helpful comments on this manuscript of Drs. G. R. Wenger, D. E. McMillan, S. H. Snodgrass and W. D. Wessinger.

REFERENCES

1. Bowen, W. D.; Hellewell, S. B.; McGarry, K. A. Evidence for a multi-site model of the rat brain sigma receptor. Eur. J. Pharmacol. 163:309–318; 1989.
2. Haertzen, C. A. Subjective effects of narcotic antagonists cyclazocine and nalorphine on the addiction research center inventory. Psychopharmacology (Berlin) 18:366–377; 1970.
3. Holtzman, S. G. Opioid and phencyclidine like discriminative effects of ditolyguanidine, a selective sigma ligand. J. Pharmacol. Exp. Ther. 248:1054–1062; 1989.
4. Litchfield, J. T.; Wilcoxon, F. A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96:99–113; 1949.
5. Lodge, D.; Anis, N. A.; Berry, S. C.; Burton, N. R. Arylcyclohexylamines selectively reduce excitation of mammalian neurons by aspartate like amino acids. In: Kamenka, J. M.; Domino, E. F.; Geneste, P., eds. Phencyclidine and related arylcyclohexylamines. Ann Arbor: NPP; 1983:595–616.
6. McCann, D. J.; Rabin, R. A.; Rens-Domiano, S.; Winter, J. C. Phencyclidine/SKF-10,047 binding sites: Evaluation of function. Pharmacol. Biochem. Behav. 32:87–94; 1989.
7. Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine and nalorphine like drugs in the nondependent and morphine dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197:517–532; 1976.
8. Matsumoto, R. R.; Hemstreet, M. K.; Lai, N. L.; Thurkauf, A.; De Costa, B. R.; Rice; K. C.; Hellewell, S. B.; Bowen, W. D.; Walker, M. W. Drug specificity of pharmacological dystonia. Pharmacol. Biochem. Behav. 36:151–155; 1990.
9. Taylor, D. P.; Dekleva, J. Potential antipsychotic BMY-14802 selectively binds to sigma sites. Drug Dev. Res. 11:65–70; 1987.
10. Vincent, J. P.; Kartalovski, B.; Geneste, P.; Kamenka, J. M.; Lazdunski, M. Interaction of phencyclidine ("angel dust") with a specific receptor in rat brain membranes. Proc. Natl. Acad. Sci. USA 76:4678–4682; 1979.
11. Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; De Costa, B.; Rice, K. C. Sigma receptors: Biology and function. Pharmacol. Rev. 42:355–402; 1990.
12. Walker, J. M.; Matsumoto, R. R.; Bowen, W. D.; Gans, D. L.; Jones, K. D.; Walker, F. O. Evidence for a role of haloperidol-sensitive sigma-'opiate' receptors in the motor effects of antipsychotic drugs. Neurology 38:961–965; 1988.
13. Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W. 1,3,D1(2-5[^{3}H]toly)guanidine: a selective sigma ligand that labels sigma-type receptors for psychotomimetic opioids and antipsychotic drugs. Proc. Natl. Acad. Sci. USA 83:8784–8788; 1986.
14. Wong, E. H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. I. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA 83: 7104; 1986.
15. Zukin, S. R.; Zukin, R. S. Specific [^{3}H]phencyclidine binding in rat central nervous system. Proc. Natl. Acad. Sci. USA 76:5372–5376; 1979.