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N-Methyl-D-Aspartate Antagonists and Drug Discrimination

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KOEK, W. N-*methyl-D-aspartate antagonists and drug discrimination.* PHARMACOL BIOCHEM BEHAV **64**(2) 275–281, 1999.—Excitatory amino acids (EAA), such as glutamate, are thought to be involved in various disorders (e.g., ischemic brain damage, epilepsy, Parkinson's disease), and EAA antagonists have been suggested as potential treatments for these disorders. Phencyclidine (PCP), with produces psychotomimetic effects in humans, has antagonist properties at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors that have been suggested to underlie some of its actions. This suggestion, and concern about possible psychotomimetic activity, has stimulated research aimed at examining to what extent the behavioral profile of other NMDA antagonists resembles that of PCP. Drug discrimination (DD) is prominent among the procedures used to carry out such comparisons. The results of clinical studies with NMDA antagonists provide feedback about the predictive validity of the DD procedures used to characterize their preclinical behavioral profile. Further, DD is used also to examine the ability of compounds to attenuate the discriminative stimulus (DS) effects of PCP-type drugs, and results of such studies have been suggested to provide evidence of antipsychotic potential. Finally, although many instances of intermediate responding in DD can be explained by low efficacy at the receptors that mediate the DS effects of the training drug, certain outcomes produced by PCP-type drugs do not offer valid measures of efficacy, and require more detailed behavioral analyzes. © 1999 Elsevier Science Inc.

Phencyclidine NMDA antagonists Drug discrimination

EXCITATORY amino acids (EAA), such as glutamate, which are among the most ubiquitous neurotransmitters, are thought to be involved in various CNS disorders. EAA exert their effects through a variety of receptors, and compounds interacting with these receptors may be of benefit in alleviating EAA-related disorders.

PCP, which produces psychotomimetic effects in humans, has antagonist properties at the *N*-Methyl-D-Aspartate (NMDA) subtype of glutamate receptors that have been suggested to underlie some of its actions. This suggestion, and concern about possible psychotomimetic side effects, has stimulated research aimed at examining to what extent the behavioral profile of other NMDA antagonists resemble that of PCP. Because of its sensitivity and pharmacological specificity, drug discrimination (DD) is prominent among the procedures used to carry out such comparisons. Stimulated by potential therapeutic applications, novel NMDA antagonists have been developed, and the results of clinical studies with these compounds provide feedback about the predictive validity of the DD procedures used to characterize their preclinical behavioral profile. Instead of attempting to cover all DD studies with NMDA and other EAA antagonists that have appeared to date, the present review describes selected DD studies with NMDA antagonists for which (clinical) data in humans are available, and will compare their preclinical DD data with reported effects in humans.

DD is used not only to examine the ability of compounds to produce PCP-like discriminative stimulus (DS) effects, but also their ability to attenuate the DS effects of PCP-type drugs. Because PCP has psychotomimetic effects in humans, the results of such latter studies have been suggested to provide evidence of antipsychotic potential. A second objective of the present review is to present some examples of this approach, which, so far, appears to have had only limited success.

The third and last part of this review will describe particular outcomes of DD studies with PCP-type compounds that do not appear to be related to their PCP-like DS effects, but may involve other mechanisms. Such outcomes, which are relevant to the interpretation of intermediate responding in DD, indicate the need to analyze behavior in DD procedures in more detail than is commonly reported.

PCP-LIKE DS EFFECTS IN LABORATORY ANIMALS, AND POSSIBLE PCP-LIKE EFFECTS IN HUMANS

The NMDA receptor complex consists of an ion channel, associated with the NMDA receptor, and with a strychnine-insensitive glycine coagonist site. Based on the site of the NMDA receptor complex with which NMDA antagonists interact, the following subtypes have been described: 1) uncompetitive, ion-channel blockers, 2) competitive receptor antag-

onists, and 3) antagonists at the glycine site. The ability of NMDA antagonists to produce PCP-like DS effects in animals and PCP-like effects in humans is reviewed here by describing these effects separately for each class of NMDA antagonists.

Uncompetitive, Ion Channel-Blocking NMDA Antagonists

Ketamine is a derivative of PCP that has been shown to produce PCP-appropriate responding in a variety of drug discrimination studies using pigeons, rats, and monkeys [e.g., (18,22,64)]. In humans, ketamine has PCP-like psychotomimetic effects, characterized by perturbed perception, attention, thinking, memory, and affect [e.g., (12)].

Dizocilpine (MK-801) has been shown to produce PCP-like DS effects in various DD studies in animals [e.g., (58,61)]. There are only a few reports, however, of its effects in humans. Troupin et al. (59) used low doses of dizocilpine as a supplemental therapy in drug-resistant epileptics, and reported rapid tolerance to its therapeutic effects. Restless disorientation and confusion were among the side effects noted with dizocilpine. In an open trial in adults with attention deficit disorder, dizocilpine appeared to improved mood more than concentration (50). Thus, although dizocilpine is often assumed to produce effects similar to those of PCP in humans, detailed published reports showing this indeed to be the case appear to be lacking.

The converse is true for cerestat (CNS-1102), which has been shown to produce PCP-like effects in humans (39,40). Data on its possible PCP-like DS effects, however, are lacking. In our laboratory, we found CNS-1102 (2.5 mg/kg) to have DS effects similar to those of PCP (2.5 mg/kg) and dizocilpine (0.04 mg/kg) in rats trained to discriminate 0.08 mg/kg dizocilpine from saline (Kleven and Koek, unpublished observations).

Low-Affinity Ion Channel Blockers

It has been suggested that compounds with low affinity for the NMDA receptor-associated ion channel, such as memantine and amantadine, may have a reduced liability to produce PCP-like side effects [e.g., (32,53)]. Memantine, however, appears to produce both PCP-like DS effects in animals [e.g., (16,41,54)] and psychotomimetic effects in humans [e.g., (51)]. This profile of memantine is not incompatible with reports that its affinity for PCP binding sites is similar to that of ketamine (32).

In contrast, amantadine, whose affinity for PCP binding sites is about 20-fold lower than that of ketamine (32), reportedly produced less than 25% PCP lever responding (41,54) in animals, and produces visual hallucinations in humans but, unlike PCP, does not exert adverse effects on cognition and memory (67).

Ibogaine, which may affect drug self-administration and withdrawal, reportedly has micromolar affinity for the channel site of the NMDA receptor complex (48) and acts as an NMDA antagonist (47). Drug discrimination studies found ibogaine to produce dizocilpine-like DS effects in mice (14); in rats and monkeys, however, ibogaine lacked PCP-like DS effects (24). In humans, ibogaine has been reported to produce a hallucinogenic state, but its acute effects are likely different from PCP, which also affects memory and cognition, and produces catatonia.

Subtype Selective NMDA Antagonists

Ifenprodil and eliprodil are NMDA antagonists with selective affinity for the NR1A/NR2B NMDA receptor subunit combination. In PCP-trained rats, neither ifenprodil (21,30) nor eliprodil (3) produced any drug-lever (DL) responding. There appears to be no evidence that ifenprodil has PCP-like effects in humans, and eliprodil reportedly does not disrupt memory and does not produce sedation, excitation, or psychotomimetic effects (46).

Competitive NMDA Antagonists

The competitive NMDA receptor antagonists, selfotel (CGS 19755), d-CPPene (SDZ EAA-494), and CPP all appear to produce PCP-like effects in humans. Selfotel reportedly produced psychotomimetic symptoms, such as agitation, hallucinations, confusion, and paranoia (17,66). D-CPPene disturbed concentration and memory, and produced sedation and ataxia (52,57). CPP has been found to produce ketamine-like psychotomimetic effects (33). In contrast with these clinical data, DD studies in animals have, in general, shown these compounds to substitute only partially for PCP-type drugs [reviewed in, e.g., (62,65)], even when the training dose was lowered (21) [in a study that found increased substitution when lowering the training dose of PCP (37), increased substitution was observed also with non-PCP-type drugs, indicating diminished pharmacological specificity]. Some of the reasons for this apparent discrepancy between preclinical and clinical data will be discussed below.

Antagonists at the NMDA Receptor-Associated Glycine Site

The glycine modulatory site of the NMDA receptor complex has attracted considerable interest because of the possibility that antagonists at this site may have less side effects than other NMDA antagonists [e.g., (20,36)].

ACEA 1021 is one of the glycine site antagonists that is in advanced clinical development, and for which clinical data are now becoming available. ACEA 1021 was found to be devoid of PCP-like DS effects (2), and to date, no psychotomimetic effects have been reported (1).

Discussion

When a compound lacks the ability to produce any drug-lever (DL) responding in PCP-trained animals, it is unlikely to produce PCP-like subjective effects in humans (e.g., ifenprodil, eliprodil). When a compound substitutes completely for PCP, it has the potential to induce PCP-like subjective effects in humans (e.g., ketamine, CNS-1102). Intermediate responding, however, is more difficult to interpret. In many, but not all, DD studies, competitive NMDA antagonists have been shown to substitute only partially for PCP or dizocilpine, and such outcomes have generally been interpreted to indicate that their potential to produce PCP-like subjective effects in humans is less than those of PCP-type, noncompetitive NMDA antagonists. The limited clinical data that are currently available suggest, however, that the subjective effects of competitive NMDA antagonists may be more similar to those of PCP than most preclinical DD data have suggested. Among the few studies that found competitive NMDA antagonists to substitute fully for PCP or dizocilpine, that by Geter-Douglas and Witkin (15) is particularly interesting, because of its suggestion that the degree of substitution may depend on the DD procedure used. Specifically, disruptive drug effects on lever-press responding, which is the behavior measured in most

studies, often prevent testing higher doses that may produce PCP-like DS effects in procedures (e.g., T-maze) less sensitive to such disruptive effects. Indeed, the extent to which competitive NMDA antagonists induce PCP-appropriate responding has been shown to depend in part on the time course of drug-induced decreases of operant responding (4).

Finally, it should be noted that NMDA antagonists may not only share DS effect with PCP, but also with ethanol. For example, ketamine, which in rats produces ethanol-appropriate responding (56), has ethanol-like subjective effects in humans (34). Thus, it would seem important to examine novel NMDA antagonists, and other compounds that decrease glutamatergic neurotransmission, not only for their ability to produce PCP-like, but also ethanol-like DS effects. An example is a study of the ability of glutamate-release inhibitors, lamotrigine and riluzole (PK-26124, RP 54274), which reportedly lack PCP-like DS effects (29,30,35), in rats trained to discriminate ethanol: lamotrigine substituted for ethanol, whereas riluzole did not (19).

ANTAGONISM OF PCP'S DS EFFECTS IN LABORATORY ANIMALS AND ANTIPSYCHOTIC POTENTIAL

The effects of PCP in humans often resemble schizophrenia [e.g., (13)]. For example, in normal volunteers, PCP can produce disordered perception, attention, affect, and thinking. In schizophrenic patients, PCP has been reported to intensify psychotic symptoms. Based on the similarity between PCP-induced psychosis and schizophrenia, it has been proposed that antagonists of PCP may be useful as antipsychotic agents.

Most animal studies have examined the ability of various agents to modify PCP-induced locomotion, stereotypy, and ataxia. In general, however, such studies are unable to distinguish between a pharmacological antagonism of the effects of PCP and, for example, interactions between the motor effects of the test compound and those of PCP [see, however, (38)]. Because of its sensitivity and pharmacological specificity, PCP DD, which affords not only a measure of DS effects, but also of effects on response rate, is thought to be helpful in identifying potential PCP antagonists.

An early example of the use of PCP DD to identify possible PCP antagonists is a study reporting that adenosine agonists attenuated the DS effects of PCP in rats (8). This finding, however, proved to be of limited generality, because these compounds were unable to attenuate the DS effects of PCP in monkeys trained with ketamine (64) and in rats trained with PCP using a procedure similar to, but not identical with that described by Browne and Welch (5). Metaphit, a proposed PCP receptor acylator, reportedly blocked PCP-induced stereotypy and ataxia in rats (10), but failed to attenuate the DS effects of PCP (or of ketamine) in rats, pigeons, and rhesus monkeys (5,31). The α_1-antagonist, prazosin, partially antagonized the DS effects of PCP in one study (60), but attenuated only the response rate effects of PCP in another (5). At present, compounds that consistently block the DS effects PCP do not appear to be available. Should such a compound be identified, it is unlikely that it would have substantial affinity for PCP binding sites, because binding to these sites, which are thought to be located in the NMDA receptor-associated ion channel, would be expected to produce effects similar to those of PCP. Instead, the compound may interfere with the expression of the effects of PCP by acting on mechanisms other than, or downstream of, ion channels associated with NMDA receptors.

More recently, a dizocilpine discrimination in rats has been proposed as an animal model to identify compounds with potential efficacy in treatment-resistant schizophrenia, based on the reported ability of clozapine, but not haloperidol, to antagonize the DS effects of dizocilpine (11). If confirmed, this latter observation, however, may not necessarily involve mechanisms underlying clozapine's antipsychotic efficacy, but conceivably could be related its α_1-adrenergic antagonist properties, which have been suggested to underlie its ability to modulate events mediated by the NMDA receptor complex (49). Using dizocilpine as training drug in mice, the proposed dopamine D_3 receptor agonist, PD 128,907 reportedly attenuated the DS effects of the training drug (63). Although these findings are interesting, it should be noted that antagonism of the DS effects of dizocilpine has been studied less extensively than that of the DS effects of PCP. Clearly, it is important not only to examine (putative) antipsychotics in dizocilpine discriminating animals, but also compounds that lack antipsychotic efficacy, in order to explore the predictive validity of the results obtained in this procedure. Recently, we obtained preliminary evidence that buspirone (0.63 mg/kg) almost completely blocked the DS effects of dizocilpine (0.08 mg/kg) in rats (Kleven and Koek, unpublished observations). Buspirone was thought to have antipsychotic potential based on preclinical studies, but was subsequently found to lack antipsychotic efficacy (55). Thus, our preliminary evidence suggests the possibility that if antagonism of the DS effects of dizocilpine is used to predict antipsychotic efficacy, buspirone may be a false positive.

A final example of a compound reportedly able to attenuate behavioral effects of PCP is the proposed sigma-selective ligand, NE-100 (42–45). PCP produces DL selection in PCP-trained rats along an inverted U-shaped dose–response curve (6,27), and recent observations from our laboratory (25) show the same to be the case for DL selection produced by dizocilpine in dizocilpine-trained rats. In these rats pretreatment with NE-100 (0.63–10 mg/kg) failed to alter markedly the ascending limb of the dose–response curve of dizocilpine, but shifted the descending limb upward, i.e., doses of dizocilpine higher than the training dose, which produced intermediate levels of DL selection when given alone, produced higher levels of DL selection in the presence of NE-100. Whereas the ascending limb of the dose–response curve of dizocilpine involves its DS effects, other mechanisms (27,28) are likely to be involved in the descending limb (25). Thus, although NE-100 did not appear to antagonize the DS effects of dizocilpine, it may have attenuated effects of dizocilpine unrelated to its DS properties that gave its dose–response curve a biphasic appearance. These latter effects are detailed below.

PCP-TYPE DRUGS CAN PRODUCE DL SELECTION UNRELATED TO DS EFFECTS

Although the outcomes of drug discrimination tests often appear to be simple, some test compounds, however, neither fully substitute for, nor completely antagonize, the training drug, but produce intermediate responding. It is helpful to assume initially that such an outcome represents shared DS effects, possibly resulting from low efficacy actions at the receptors that mediate the DS effects of the training drug. This assumption can be examined further by studying, for example, whether a compound that produces intermediate responding when given alone partially antagonizes the training drug, and by examining whether the maximum level of drug-appropriate responding that such a compound produces can be enhanced by decreasing the training dose and attenuated by increasing the training dose. These predictions were exam-

ined in a series of experiments in animals trained to discriminate opioids from saline, in an effort to analyze further the intermediate responding produced by partial opioid agonists, such as cyclazocine, and that produced by phencyclidine (PCP)-like *N*-methyl-D-aspartate (NMDA) antagonists, such as dizocilpine. In contrast to the results obtained with cyclazocine, the results obtained with the PCP-like NMDA antagonists failed to support the hypothesis that low efficacy actions at opioid receptors underlies their ability to produce intermediate responding in opioid-trained animals (26,27). Further, dizocilpine produced intermediate responding in opioid-trained animals [see also (7)], and in several pharmacologically unrelated drug discriminations (28). This intermediate responding was frequently associated with a particular pattern of other behavioral effects (i.e., a high percentage responses on the nonselected lever, both before and after lever selection occurred, and a long selection latency; see example in Fig. 1) that differed from the pattern observed with partial agonists that likely produce partial generalization by mimicking the pharmacological actions of the training drug. Thus, the intermediate responding produced by PCP-type drugs can involve pharmacological effects that differ from those of the training drug, and behavioral mechanisms unrelated to stimulus generalization.

Although efficacy at the receptors that mediate the DS effects of the training drug has been shown to explain many of the instances of intermediate responding in drug discrimination, certain outcomes, exemplified by those obtained with PCP-type drugs, are less readily accommodated. Such outcomes do not appear to offer valid measures of efficacy at the receptors mediating the DS effects of the training drug, and require more detailed behavioral analyses. Commonly, drug discrimination studies report only measures of drug-appropriate responding and of overall response rate. Such measures fail to discriminate between the effects of the low efficacy opioid agonist, cyclazocine, and the PCP-type drug, dizocilpine,

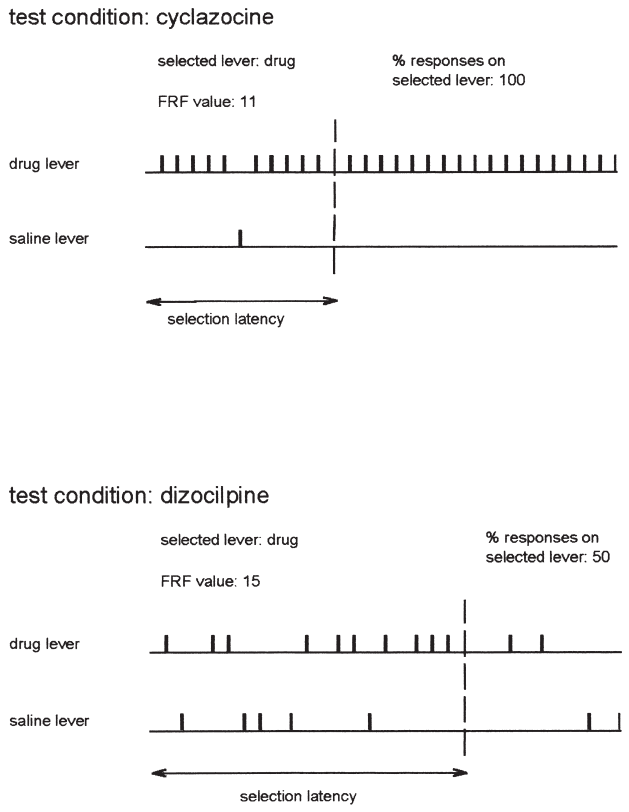

FIG. 1. Schematic representation of the behavioral effects of the low efficacy opioid agonist, cyclazocine (upper panel), and the phencyclidine-like compound, dizocilpine, in rats trained to discriminate 0.04 mg/kg of the high-efficacy opioid, fentanyl, from saline using a two-lever, fixed-ratio 10 (FR10) procedure. In contrast to cyclazocine, which has effects similar to those observed during tests of 0.04 mg/kg fentanyl, dizocilpine typically produces lever selection (i.e., the lever on which 10 responses accumulate first) associated with a high FRF value (sum of responses made on either lever before the first reinforcement occurred), a long selection latency (LAT), and a low percentages of responses on the selected lever (RSL, based on responses made after lever selection occurred, and calculated by dividing the number of responses on the selected lever by the sum of responses made on either lever and multiplying the result by 100).

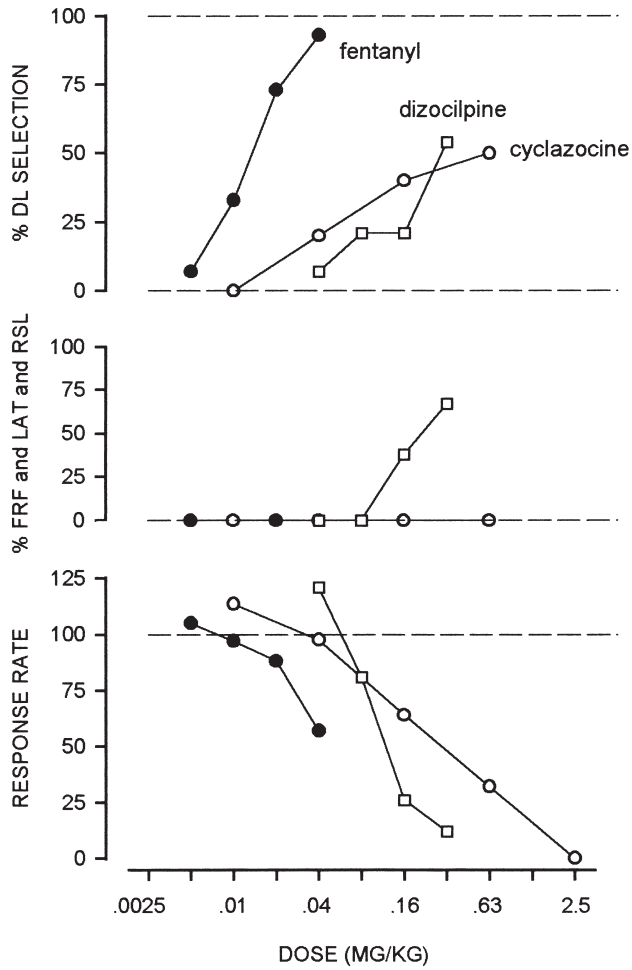

FIG. 2. Effects of the low efficacy opioid agonist, cyclazocine (upper panel), and the phencyclidine-like compound, dizocilpine, in rats trained to discriminate 0.04 mg/kg of the high-efficacy opioid, fentanyl, from saline using a two-lever, fixed-ratio 10 (FR10) procedure. Vertical axes: lever selection (percentage of rats selecting the DL), incidence of the simultaneous occurrence in the same animals of FRF $>$ 11, LAT $>$ 90 s and RSL $<$ 99 (as a percentage of the number of lever selections that occurred), and overall response rate (as a percentage of saline control). For further details, see legend to Fig. 1. Data are replotted from (27), and unpublished observations (Colpaert, Kleven, and Koek).

in rats trained to discriminate 0.04 mg/kg of the high efficacy opioid, fentanyl, from saline (Fig. 2). Differences between cyclazocine and dizocilpine become apparent only when one considers their effects on FRF values, lever selection latencies, and on responding on the selected lever. In contrast to cyclazocine, dizocilpine produced DL selection only at doses that increased the percentage of animals that simultaneously exhibited high FRF values (FRF $>$ 11), long selection latencies (LAT $>$ 90 s), and low percentages of responses on the selected lever (RSL $<$ 99). Such data suggest the potential utility of these additional measures to distinguish low efficacy at the receptors that mediate the DS effects of the training drug from other mechanisms by which intermediate responding can occur in drug discrimination studies.

Using these additional measures not only helps to differentiate shared DS effects from other mechanisms underlying DL responding, but also allows one to examine these other mechanisms in more detail. At the behavioral level, state dependency has been suggested to provide a mechanism by which test drugs can produce intermediate responding unrelated to their DS effects [e.g., (9)]. At the pharmacological level, the aforementioned finding that NE-100 attenuates the disruptive effects of doses of dizocilpine higher than the training dose (25) is consistent with the finding that the sigma ligand, NE-100, diminished the ability of PCP to increase choice reaction time and to decrease choice accuracy (23), and suggests the possibility that sigma receptors may be involved in the modulation of these effects.

SUMMARY AND CONCLUSIONS

Because PCP, which produces psychotomimetic effects in humans, has NMDA antagonist properties, DD has been used to examine the possible PCP-like DS effects of other NMDA antagonists. In general, compounds that substitute fully for PCP in animals (e.g., ketamine, CNS-1102) exert PCP-like effects in humans. Further, NMDA antagonists that lack PCP-like DS effects in animals (e.g., ifenprodil, eliprodil) do not appear to produce PCP-like untoward effects in humans. Some compounds that often produce only intermediate responding in PCP-trained animals (e.g., selfotel), produce, however, symptoms very similar to those of PCP in humans. It appears, therefore, that not only full DL responding in PCP-trained animals, but also partial DL responding, may indicate the potential to produce PCP-like effects in humans. Detailed results of clinical studies with NMDA antagonists acting at the glycine modulatory site (e.g., ACEA 1021), which appear to be unable to produce PCP-like DS effects in animals (2), will allow further examination of the extent to which outcomes in PCP DD in animals are predictive of PCP-like effects in humans.

Because PCP has psychotomimetic effects in humans, antagonism of its effects in animals is thought to indicate antipsychotic potential. Although some (putative) antipsychotics have been reported to be able to antagonize the DS effects of PCP in animals (e.g., adenosine analogs, clozapine), the generality of these findings could not, or has not yet been established. Even if confirmed, the predictive validity of such findings is limited by the observation that buspirone, which appears to attenuate the DS effects of the PCP-like compound, dizocilpine, does not have marked antipsychotic efficacy.

PCP-like compounds can produce intermediate levels of DL selection apparently without sharing DS effects with the training drug, but by disrupting discriminative responding. The sigma ligand, NE-100, attenuated the disruptive, but not the DS effects of dizocilpine. The behavioral measures described here may help to identify disruptive effects that can underlie intermediate DL responding, and to further examine their underlying behavioral and pharmacological mechanisms.

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