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ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2008) 189–195
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Antagonism of phencyclidine-induced stimulus control in the rat by other psychoactive drugs

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Received 6 April 2007; received in revised form 6 July 2007; accepted 6 July 2007
Available online 15 August 2007

Abstract

It has been observed that agents with agonist activity at 5-HT_{2A} receptors prevent neurotoxicity induced by the non-competitive NMDA antagonist, dizocilpine (MK-801). Subsequent behavioral studies reported complete antagonism by LSD and DOM of the stimulus effects of the related NMDA antagonist, phencyclidine [PCP]. The present study sought to extend those observations to include other psychoactive drugs. Male F-344 rats were trained in a 2-lever, fixed-ratio 10, food-reinforced task with PCP (3.0 mg/kg; IP; 30 min pretreatment) as a discriminative stimulus. Tests of generalization were then conducted using the training dose of PCP in combination with a range of doses of DOM, LSD, D-amphetamine, MDMA, psilocybin, buspirone, and GHB. All of the drugs tested in combination with PCP produced a statistically significant diminution of PCP-appropriate responding but for none was antagonism complete. These data, obtained using a stimulus control model of the hallucinogenic effects of PCP, fail to support the hypothesis that LSD and DOM completely antagonize stimulus control by PCP. Instead, the data suggest complex interactions between PCP-induced stimulus control and a variety of psychoactive drugs including GHB, an agent with no known affinity for serotonergic receptors.

Keywords: Lysergic acid diethylamide (LSD); Phencyclidine (PCP); (−)-2,5-dimethoxy-4-methylamphetamine (DOM); D-amphetamine; Methylenedioxymethamphetamine (MDMA); Psilocybin; Buspirone; *Gamma*-hydroxybutyrate (GHB); Drug discrimination; Rat

1. Introduction

In the years following the pioneering studies of Overton (1974, 1998) and Barry (1974; Barry et al., 1965), drug-induced stimulus control has proven to be a powerful tool for the characterization of psychoactive drugs (Balster, 1990; Meert and Stolerman, 1999; Winter, 1974, 1978). Many of the results have been as expected, *i.e.*, in agreement with conclusions drawn from studies using other methods, both behavioral and non-behavioral. Traditional classifications of drugs are not violated; in terms of their stimulus effects, opiates resemble opiates, depressants resemble depressants, stimulants resemble stimulants, and hallucinogens resemble hallucinogens. Likewise, drug interactions are often as predicted, *e.g.*, morphine readily establishes stimulus control in rats and its stimulus effects are completely antagonized by naloxone. However, as data have accumulated and as the study of stimulus control has been refined over the decades, deviations from these neat classifications have emerged. These include apparently non-essential components (Winter, 1984), odd generalizations (Winter and Rabin, 1992), and intermediate degrees of antagonism (Winter et al., 2004) and substitution (Fantegrossi et al., 2006).

A substantial body of evidence from studies in rodents supports the notion that serotonergic agents may influence glutamatergic function and *vice versa*. Thus, for example, it has been observed that the stimulus effects of DOM and of LSD are potentiated by PCP (Winter et al., 2000a, 2004) and that head twitches induced by serotonergic agonists are enhanced by NMDA antagonists (Kim et al. 1998, 1999; Dall'Olio et al., 1999). In addition,

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doi:10.1016/j.pbb.2007.07.007

stimulus control by PCP is potentiated by the selective serotonin reuptake inhibitor, citalopram (Winter et al., 2005). Furthermore, the $mGlu_{2/3}$ receptor ligands, LY341495 and LY379268, which increase and decrease, respectively, glutamate release *in vivo*, were found to increase and decrease, respectively, stimulus control by LSD (Winter et al., 2004). The selective 5-HT_{2A} antagonist, M100907, and the serotonergic atypical antipsychotic agent, clozapine, block a variety of PCP-induced effects including hyperlocomotion (Maurel-Remy et al., 1995; Swanson and Schoepp, 2002), deficits in pre-pulse inhibition (Yamada et al., 1999), immobility in a forced swim test (Corbett et al., 1999), and the expression of the immediate early gene *c-fos* (Habara et al., 2001). Direct neurochemical support is provided by the results of studies using *in vivo* microdialysis. Scruggs et al. (2003) observed that DOI, the iodo analog of DOM, increases glutamate efflux in rat somatosensory cortex. In our laboratories, it was found that LSD increases extracellular glutamate in rat prefrontal cortex and that this effect is fully antagonized by the selective 5-HT_{2A} antagonist, M100907 (Muschamp et al., 2004). Of direct relevance to the present investigation, neurotoxicological studies found that agents with agonist activity at 5-HT_{2A} receptors, including LSD and DOM, prevent NMDA antagonist-induced cytopathological changes in cerebrocortical neurons of the rat (Farber et al, 1998). Similarly, using neuronal primary cultures from neonatal rats, Gondolfi et al. (2002) observed protection against cell death due to high concentrations of glutamate by DOI and by 8-OH-DPAT, an agonist at 5-$HT_{1A/7}$ receptors. Against this background, the report by West et al. (2000) that stimulus control by PCP is completely antagonized by DOM and by LSD, though unprecedented, is not without a theoretical foundation.

In the present investigation, PCP-induced stimulus control was established in rats. Subsequent experiments tested the interactions between PCP and the serotonergic agents, LSD, DOM, psilocybin, and buspirone. In addition, interactions with PCP were tested with the dopaminergic/serotonergic drugs, D-amphetamine and MDMA, as well as with GHB, a drug thought to act *via* non-serotonergic mechanisms (Bernasconi et al., 1999; Carter et al., 2004; Winter, 1981).

2. Methods

2.1. Animals

A total of 24 male Fischer 344 rats were obtained in two groups of 12 each at an age of approximately 6 weeks from Harlan Sprague–Dawley Inc. (Indianapolis, IN, U.S.A.). Subjects were housed in pairs under a 12-h light–dark cycle beginning at 6:00 a.m. and allowed free access to water in their home cages. All training and testing took place during the light cycle. Caloric intake was controlled to maintain a mean body weight of approximately 300 g. Subjects were fed standard rat chow following experimental sessions. Caloric control and decreased frequency of food availability has been shown to lengthen the life span and decrease the incidence of a variety of pathologies in rats (Goodrick et al., 1983; Beauchene et al., 1986; Keenan et al., 1994). Animals used in these studies were maintained in accordance with U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals as amended August 2002. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University at Buffalo.

2.2. Apparatus

Two small animal test chambers (MED Associates ENV-008) were used for all experiments. These were housed in larger light-proof, sound-insulated boxes which contained a house light and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper which delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water. Sessions were managed by a microcomputer using operant conditioning control software (MED-PC State Notation, Version IV).

2.3. Training procedures

After learning to drink from the dipper, rats were trained to press first one and then the other of the two levers. The number of responses for each reinforcement was gradually increased from 1 to 10. During this time, the reinforced lever was alternated on a random basis. All subsequent training and testing sessions used a fixed-ratio 10 (FR10) schedule of reinforcement. Discrimination training was then begun. The initial group of 12 subjects was trained to discriminate PCP (3.0 mg/kg, 30 min pretreatment time, IP; $N=12$) from vehicle as described previously (Hirschhorn and Winter, 1971; Fiorella et al., 1995; Winter et al., 2004). Subsequently, a second group of 12 subjects was trained at a dose of 2.5 mg/kg using a pretreatment time of 15 min (West et al., 2000). Following the administration of drug, every tenth response on the drug-appropriate lever was reinforced. Similarly, responses on the vehicle-appropriate lever were reinforced on a FR10 schedule following the injection of vehicle. For half of the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, drug and vehicle were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate lever, *i.e.*, no more than 2 incorrect responses prior to completion of the FR10 on the correct lever.

2.4. Tests of antagonism

After stimulus control with PCP was well established, tests of antagonism were conducted once per week in each animal. Tests were balanced between subjects trained on the previous day with vehicle and drug, respectively. During test sessions, no responses were reinforced and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time. Data for any subjects failing to emit 10 responses

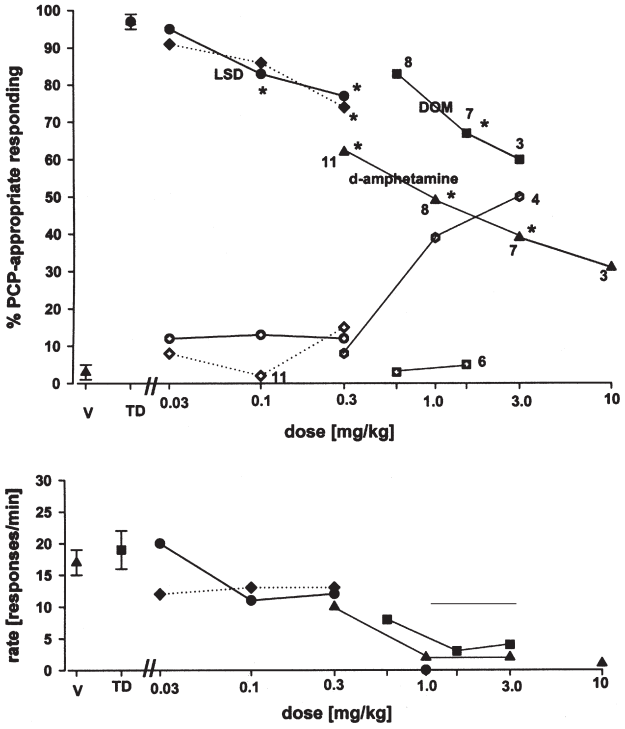

Fig. 1. Dose–response relationships for LSD (circles, diamonds), (−)-DOM (squares), and D-amphetamine (triangles) alone (crossed figures) and in combination with PCP (3 mg/kg; closed figures) in rats trained with PCP (3.0 mg/kg) as a discriminative stimulus. For LSD, two different pretreatment times were used: 60 min (dotted lines) and 15 min (solid lines), *i.e.*, before and after the administration of PCP. The points at V and TD on the *abscissa* are for vehicle and PCP training sessions, respectively. With the exception of the training sessions, each point represents the mean of one determination in each of 12 rats. A number next to a data point indicates the number of subjects completing the session if less than 12. *Ordinate*: upper panel: percent PCP-appropriate responding; lower panel: rate expressed as responses per minute. *Abscissa*: dose plotted on a log scale. *Statistically significantly different from PCP alone; $P<0.05$.

within the constraints of the 10 min test session were not considered in the calculation of the percent drug-appropriate responding but were included in the analysis of response rates. The effects of other drugs on PCP-induced stimulus control were assessed by co-administration of PCP (3.0 mg/kg, 30 min pretreatment) and a second drug as previously described (Winter et al., 2000a). With two exceptions, a pretreatment time of 15 min was used for all interacting drugs, *i.e.*, 15 min following PCP. DOM was injected 75 min before testing, *i.e.*, 45 min before PCP. Two sets of experiments were conducted with LSD, the first using a 15 min pretreatment time, *i.e.*, following PCP and the second a 60 min pretreatment time, *i.e.*, 45 min before PCP administration. The latter LSD experiments were conducted in a second group of rats trained with a PCP pretreatment time of 15 min. For purposes of discussion of data resulting from tests in which antagonism of stimulus control occurs (Winter et al., 2000b), an intermediate degree of antagonism is here defined as less than 80% training drug-appropriate responding and significantly different from both training conditions. Complete antagonism is defined as <20% drug-appropriate responding and not significantly different from the vehicle training condition.

2.5. Drugs

Lysergic acid diethylamide ((+)-LSD (+)-tartrate (2:1)), (−)-DOM, phencyclidine HCl, D-amphetamine sulfate, (+/−)-MDMA, and psilocybin were generously provided by the National Institute on Drug Abuse, Rockville, MD, USA. Buspirone and *gamma*-hydroxybutyrate sodium salt were purchased from Tocris and Sigma, respectively.

2.6. Statistical analysis

The statistical significance of the interactions between PCP and other drugs was assessed by comparing PCP-appropriate responding following the training dose of PCP with the corresponding value following the combination of PCP and a second drug. A paired Student's *t*-test was employed. In the event that the data for any given comparison failed to satisfy the criterion for normality of distribution, a signed ranks test was employed. Differences were considered to be statistically significant if the probability of their having arisen by chance was <0.05. All analyses were conducted using SigmaStat 3.1 for Windows™ (Jandel Scientific Software, San Rafael, CA). Control data were repeated for each comparison and statistical analyses were applied using the appropriate control sessions. However, for purposes of clarity, mean values for control data are shown in all figures.

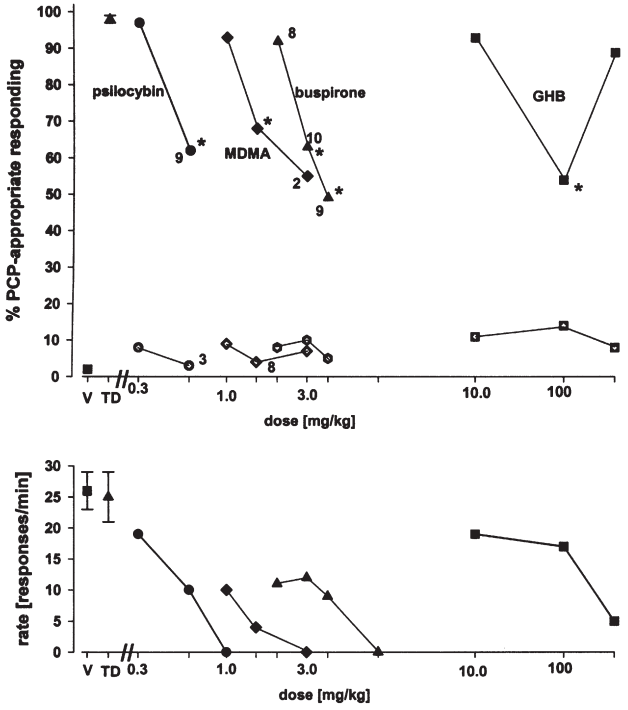

Fig. 2. Dose–response relationships for psilocybin (circles), MDMA (diamonds), buspirone (triangles), and GHB (squares) alone (crossed figures) and in combination with PCP (3 mg/kg; closed figures) in rats trained with PCP (3.0 mg/kg) as a discriminative stimulus. All other details are as in Fig. 1.

3. Results

Fig. 1 presents the results of experiments examining the effects of a range of doses of (−)-DOM, LSD, and D-amphetamine either alone or in combination with the training dose of PCP. For each of the drugs tested, one or more doses in combination with PCP produced a statistically significant decrease in PCP-appropriate responding (upper panel, solid figures). In no instance was complete antagonism observed. Rates of responding were well maintained for LSD but both DOM and D-amphetamine produced dose-related suppression (lower panel) and, at the higher doses, not all subjects completed the test session. Complete suppression of responding occurred at a dose of each of the interacting drugs 1/2 log unit higher than the maximum dose shown in the upper panel of Fig. 1. The interaction of LSD with PCP was initially examined in a group trained with PCP (3.0 mg/kg) using a 30 min pretreatment time while LSD was administered 15 min before testing, *i.e.*, following PCP (Fig. 1, circles connected by a solid line). A second group was then trained using a dose of PCP of 2.5 mg/kg and a pretreatment time of 15 min (West et al., 2000). In the latter group, LSD was administered 60 min before testing (West et al., 2000), *i.e.*, prior to the injection of PCP (Fig. 1, diamonds connected by a dotted line). The results were indistinguishable. Also tested in the latter group of rats were the effects of (−)-DOM, LSD, and D-amphetamine when administered alone (upper panel, open figures). Only for D-amphetamine was there an indication of partial agonist activity which might account for an intermediate degree of antagonism of PCP (Eckler et al., 2003).

The results of comparable experiments in which psilocybin, MDMA, buspirone, and GHB were administered either alone (upper panel, open figures) or in combination with the training dose of PCP (upper panel, solid figures). One or more doses of each of the drugs tested produced a significant decrease in PCP-appropriate responding but in no case was complete antagonism observed. With the notable exception of GHB, the degree of antagonism of the stimulus effects of PCP was correlated with suppression of the rate of responding. When given alone, no evidence of partial agonist activity was seen (upper panel, open figures).

In Figs. 1 and 2, with the exception of the points at a dose of LSD of 0.1 mg/kg and a dose of psilocybin of 0.6 mg/kg, for which signed ranks tests were used, all conclusions of statistical significance were on the basis of paired Student's *t*-tests.

4. Discussion

In the years following the first reports of the ability of phencyclidine to induce stimulus control and state-dependent learning (Overton, 1973, 1975; Jarbe and Henriksson, 1974; Jarbe et al., 1975), several hundred studies appeared in which PCP was either trained as a discriminative stimulus or examined in animals trained with other psychoactive drugs (Stolerman and Kamien, 2005). The basis for this intense interest lies largely in the psychotomimetic properties of PCP noted above and in the hypothesis that PCP might act as a neuroprotectant in conditions such as ischemic stroke in which hyperglutamatergia is thought to be a factor (Kornhuber and Weller, 1997; Klein et al., 1999). Numerous attempts have been made to identify drugs which might either (a) mimic PCP in blocking the neurotoxic effects of glutamate or (b) antagonize the effects of PCP and thus constitute potential antipsychotic agents (Bakshi and Geyer, 1995; Corbett et al., 1995; Deutsch et al., 2002). However, based upon the prevailing hypothesis that the PCP receptor is located within the *N*-methyl-D-aspartate (NMDA) receptor-gated ion channel (Wood et al., 1987; Javitt et al., 1994; O'Donnell and Grace, 1998), it is difficult to conceptualize a drug able to exclude PCP from its receptor without itself blocking the channel and thus mimicking the behavioral effects of PCP. Nonetheless, numerous drugs have been reported to diminish psychomotor activation by PCP (Maurel-Remy et al., 1995; Klamer et al., 2005; Podhorna and Didriksen, 2005). In contrast, an antagonist of the stimulus effects of PCP has been much more elusive (Poling et al., 1979; Willetts and Balster, 1988; Koek, 1999). Though instances of partial antagonism have been reported (Beardsley and Balster, 1988; Doty et al., 1994; Koek, 1999), the report by West et al. (2000) was the first to demonstrate complete antagonism.

The observation that vehicle-appropriate responding may occur despite the administration of a drug in a dose adequate, under other circumstances, to exert stimulus control, has led to a speculation which we termed the third state hypothesis: an animal trained with drug X versus vehicle will respond in a fashion appropriate for the vehicle condition when presented with drug-induced stimuli which resemble neither those of drug X nor those of vehicle (Frey and Winter, 1978; Winter, 1978). This hypothesis adequately explains, for example, the observation that rats trained with ethanol versus vehicle continue to yield vehicle-appropriate responding when cross-tested with doses of morphine known to exert stimulus control when paired with vehicle (Winter, 1975). The third state hypothesis may also be invoked in instances of antagonism of drug-induced stimulus control. In a typical test of antagonism, rats are trained with drug X versus vehicle and combinations of drug X and a purported antagonist of X, drug Z, are then cross-tested. Responding appropriate for the vehicle condition may be interpreted as pharmacological antagonism of the effects of the stimulus effects of drug X by drug Z. However, the third state hypothesis offers an alternative explanation: vehicle-appropriate responding results not from direct pharmacological antagonism but from a third stimulus state induced by the combination of drug X and drug Z.

Interactions of the type described for the third state hypothesis have most often been discussed in terms of a hypothetical construct variously referred to as stimulus masking or perceptual blocking in which one stimulus prevents the perception of a second, concurrently presented stimulus. Investigations of the concept of the stimulus masking in the context of drug-induced stimulus control have yielded both positive (Gauvin and Young, 1989; Gauvin et al., 1994; Koek et al., 2006) and negative (Overton, 1983; McMillan and Li, 2004) results. Given the disparate pharmacological mechanisms by which the interacting drugs presented in Figs. 1 and 2 are presumed to act, stimulus masking provides a convenient

explanation for the intermediate degree of antagonism of PCP by each of these agents. However, the conclusion that stimulus masking has occurred because a plausible pharmacological mechanism is not at hand is weakened by the distinct possibility that such mechanisms are yet to be discovered. For example, we have recently shown significant, albeit partial, antagonism of the stimulus effects of LSD by an agonist at $mGlu_{2/3}$ receptors and have argued that the effect is due to functionally significant serotonergic/glutamatergic interactions at the neuronal level (Winter et al., 2004).

Drugs which have affinity for a given receptor but which are neither full agonists nor pure antagonists, *i.e.*, their intrinsic activity is less than 1.0 but greater than 0.0, are referred to as partial agonists or mixed agonist/antagonists (Winter, 1995). The latter term emphasizes that a partial agonist may sometimes function as an antagonist. Examples from the drug discrimination literature are provided by the interaction of nalorphine with morphine (Holtzman, 1983) and of nefazodone with DOM (Eckler et al., 2003). In seeking an explanation for the data shown in Figs. 1 and 2, the agonist activity of each of the interacting drugs was examined. Only for D-amphetamine was any evidence of partial agonist activity detected. With exception of LSD, all instances of partial antagonism of PCP seen in Figs. 1 and 2 were accompanied by dose-related decreases in rates of responding and the failure of all animals tested to complete the sessions. The precise impact of a reduced response rate on stimulus control is unknown but in a review of the use of drug discrimination in the study of NMDA antagonists Koek (1999) suggested that intermediate responding might involve mechanisms unrelated to stimulus generalization.

In seeking to reconcile the present observation of partial antagonism of PCP by LSD and DOM with the complete antagonism reported by West et al. (2000), a number of procedural differences must be noted. Thus, West et al. employed water deprivation, an FR20 schedule of reinforcement, a training dose of 2.5 mg/kg of PCP, and a pretreatment time of 15 min. These contrast with the present use of food deprivation, an FR10 schedule of reinforcement, a training dose of 3.0 mg/kg, and a 30 min pretreatment time. In addition, while West et al. administered LSD prior to PCP, the initial tests in the present study reversed that order (Fig. 1, closed circles, solid line). To address the question of whether these procedural differences might account for the very modest effects of DOM and LSD seen in the present results and the complete blockade of PCP by these agents as reported by West et al. (2000), a second group of rats was trained with a dose of PCP of 2.5 mg/kg using a 15 min pretreatment time and LSD was given prior to PCP. The results shown in Fig. 1 (closed diamonds, dotted line) were indistinguishable from the earlier data (Fig. 1, closed circles, solid line).

In summary, the present data are amenable to no simple interpretation. While there is little doubt that the stimulus effects of PCP were antagonized by each of the agents tested, all effects were intermediate in nature and, for all but GHB, the combinations were accompanied by decreased rates of responding. Given the complex nature of GHB's effects (Wong et al., 2004; Carter et al., 2004; Snead and Gibson, 2005), extensive speculation is not warranted at this time but the present findings suggest the possibility that $GABA_A$, $GABA_B$, and, indirectly, dopaminergic receptors may play a role in the interaction of GHB with PCP. Whether the observed diminution of PCP-appropriate responding by each of the psychoactive drugs examined represents either direct or indirect interactions with NMDA receptors remains to be established. The present data do not challenge an earlier conclusion that drugs fully able to block the stimulus effects of PCP are not yet available (Koek, 1999).

Acknowledgments

This study was supported in part by U.S. Public Health Service Grant DA 03385. I thank B. A. Winter for technical support.

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