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

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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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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