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Examining the reinforcement-enhancement effects of phencyclidine and its interactions with nicotine on lever-pressing for a visual stimulus

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HIGHLIGHTS

- PCP increased lever-pressing for a visual stimulus.
- Two doses of nicotine increased lever-pressing for a visual stimulus.
- The combination of PCP and nicotine did not increase lever-pressing.
- The effect of PCP on lever-pressing may be due to motor activation.

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ABSTRACT

Nicotine is a widely-abused drug, yet its primary reinforcing effect does not seem potent as other stimulants such as cocaine. Recent research on the contributing factors toward chronic use of nicotine-containing products has implicated the role of reinforcement-enhancing effects of nicotine. The present study investigates whether phencyclidine (PCP) may also possess a reinforcement-enhancement effect and how this may interact with the reinforcement-enhancement effect of nicotine. PCP was tested for two reasons: (1) it produces discrepant results on overall reward, similar to that seen with nicotine and (2) it may elucidate how other compounds may interact with the reinforcement-enhancement of nicotine. Adult male Sprague–Dawley rats were trained to lever press for brief visual stimulus presentations under fixed-ratio (FR) schedules of reinforcement and then were tested with nicotine (0.2 or 0.4 mg/kg) and/or PCP (2.0 mg/kg) over six increasing FR values. A selective increase in active lever-pressing for the visual stimulus with drug treatment was considered evidence of a reinforcement-enhancement effect. PCP and nicotine separately increased active lever pressing for a visual stimulus in a dose-dependent manner and across the different FR schedules. The addition of PCP to nicotine did not increase lever-pressing for the visual stimulus, possibly due to a ceiling effect. The effect of PCP may be driven largely by its locomotor stimulant effects, whereas the effect of nicotine was independent of locomotor stimulation. This dissociation emphasizes that distinct pharmacological properties contribute to the reinforcement-enhancement effects of substances.

1. Introduction

Tobacco use is a costly and deadly health problem in the United States and globally. Every year, more Americans die from tobacco related disease than the total number of US casualties across the entirety of World War II [57]. Scientists generally agree that nicotine is the main constituent of tobacco to which users develop dependence [43,58,39,54]. This agreement is notable in light of the growing literature suggesting that nicotine may have limited primary reinforcing effects [21,16,11,50,28,22].

One possible mechanism that may bridge the gap between limited reinforcing effects and the prevalence of chronic tobacco use is the reward or reinforcement-enhancement effect of nicotine. For the smoker, this means that other reinforcers ongoing while smoking (i.e., self-administering nicotine) may be more potent than when not smoking (see [11] for a review). In laboratory studies, this effect is shown by increased operant responding in rodents for a variety of rewards such as food [6,49] and visual stimuli [21,7] after nicotine exposure. In addition, this effect is not specific to

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non-human animals, as increased levels of responding for music has been shown in humans after nicotine exposure [51]. Importantly, this enhancement effect on operant responding by nicotine appears to be indicative of a change in the value of maintaining reinforcement, rather than the result of the locomotor stimulating properties of nicotine cf. [20,6,7].

This reinforcement-enhancement effect has been seen with a number of drugs other than nicotine; these include caffeine, amphetamine, cocaine, and pipradrol [56,29,52,53,8,9]. Notably, this effect has not been tested in phencyclidine (PCP). The importance of examining reinforcement-enhancement in PCP is twofold: (1) studies on the primary reinforcer value of phencyclidine have yielded discrepant results in rodents [30,2,41,13,12,17,44,19,5,34] and (2) PCP exposure is a commonly used preclinical model of positive, negative and cognitive symptoms of schizophrenia in rodents and schizophrenia has a particularly high incidence of comorbidity with nicotine dependence [45,37,36,42,31,48].

Nicotine and PCP share similarities with respect to abuse liability. Both are abused by humans although their primary reinforcing properties could be considered to be relatively weak. Though humans, primates and rodents will self-administer PCP, the rate of self-administration is relatively low in comparison to other drugs of abuse such as opiates and stimulants [46,47,19,4,14]. Further, self-administration of PCP in rodents has also been particularly difficult to find [17]. In other experimental situations, conclusions regarding the overall rewarding effect of PCP have been mixed. Intracranial self-stimulation tasks have shown an increase and decrease in stimulation thresholds depending on the time point studied and measurement procedure, suggesting a decrease and increase in reward-related behavior, respectively [2,41,12,13]. In addition, acute and chronic exposure to PCP in a sucrose-licking task found no effect on the total amount of sucrose consumed separate from motor confounds [44]. Given the abuse liability of PCP, the divergent findings with PCP on reward-related behaviors suggest an additional mechanism might be important.

It is also unclear whether there is an interaction between the reinforcement-enhancement effect in nicotine and other drugs. Nicotine (in tobacco form) is widely used in conjunction with other drugs such as alcohol and cocaine [25,23]. Notably, rates of smoking are 2–4 times higher in patients with another substance-use disorder [26,27,10,38]. There has been little attention to how the reinforcement enhancement effects of nicotine interact with the effects of other drugs of abuse. To this end, the present study examined whether PCP shows a reinforcement-enhancement effect similar to that of nicotine and whether the combination interacts in a unique manner to alter reinforcer enhancement effects in rats. Lever-pressing for a visual stimulus was trained in drug-naïve rats and then tested after treatment with nicotine, PCP, or nicotine plus PCP. Previous studies in our lab using a similar procedure found robust differences between nicotine- and saline-treated rats [6,7]. If PCP has a reinforcement–enhancement effect, we should observe selective increases in active-lever pressing maintained by visual stimuli, similar to that found with nicotine. If PCP alters the reinforcement-enhancement effect of nicotine, the rats that received the combination should differ from the nicotine alone and PCP alone groups. An increase would suggest a synergism (e.g., summative effect), whereas, a decrease would suggest interference (e.g., antagonism).

2. Materials and methods

2.1. Subjects

Forty-eight adult male Sprague–Dawley rats (226–250 g upon arrival, Charles River, Portage, MI) were used. One rat was unable to complete the study and was not included in the analysis. Rats were individually-housed in clear rectangular polycarbonate tubs (48.3 cm × 26.7 cm × 20.3 cm) under 12 h light/dark conditions (light on between 6:30 am and 6:30 pm). Room temperature was maintained at 22 ± 1° C with a relative humidity of 45–60%. Water was continuously available in the home cage. Access to food was restricted to maintain rats at 90% of their free-feeding weight. After four weeks, the target weight was increased by 2 g. Animals were allowed 5 days of habituation to the animal facility before being used in experiments. During the final two days of this habituation period, each experimenter handled each rat for approximately 2.5 min per day. All experiments were performed during the light cycle and all procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska–Lincoln.

2.2. Drugs

Phencyclidine hydrochloride (PCP, received from the NIDA Chemical Synthesis and Drug Supply Program) was dissolved in 0.9% saline (w/v). (−) Nicotine tartrate salt (Sigma, St. Louis, MO) was dissolved in 0.9% saline and adjusted to a pH of 7.0 ± 0.2 with a dilute NaOH solution. Saline, nicotine, and PCP were all administered subcutaneously. Nicotine dose was based on previous research showing that 0.4 mg/kg nicotine produced a robust reinforcement-enhancement effect [6,7]. The dose of PCP was 2.0 mg/kg and was chosen based on pilot data suggesting that this dose would not significantly differ from other doses on locomotor activity or operant behavior measures and has been frequently used to produce psychoactive effects of PCP [33,55,18,35,59]. All drugs were administered at a volume of 1 ml/kg.

2.3. Apparatus

Sessions were conducted in eight conditioning chambers (ENV-008CT; Med Associates, Inc. St. Albans, VT; 30.5 × 24.1 × 21.0 cm, l × w × h) enclosed in light- and sound-attenuating cubicles fitted with a fan used to mask noise and provide airflow. The sidewalls of the chambers were aluminum while the ceiling and front and back walls were clear polycarbonate. One sidewall featured a dipper receptacle, occupying a 5.2 × 5.2 × 3.8 cm (l × w × h) recessed space, into which a dipper arm when raised provided 0.1 ml of 26% sucrose solution (w/v) into the receptacle. Retractable levers were featured on either side of the dipper receptacle, approximately 5 cm from the chamber floor. White 28 V DC lamps (100 mA) were located 3 cm above each lever, which will be referred to as cue lights. Two external 28 V 100 mA DC lamps were also located above the chamber but within the sound attenuating cubicle, which will be referred to as the house light. An infrared emitter/detector unit positioned 4 cm above the rod floor bisected the chamber 14.5 cm from the sidewall featuring the dipper receptacle monitored general locomotor activity during experimental sessions. A computer running Med Associates interface and software (MedPC for Windows, IV) controlled stimulus presentations and recorded data.

2.4. Procedure

Lever-press training: All rats were first trained to lever-press maintained by sucrose in four consecutive sessions, approximately an hour in length. During these sessions, non-contingent sucrose was available on a variable time (VT) schedule, starting with a VT 30 s on day one and fading to VT 180 s on the final day. Sucrose was also contingently available during these sessions on a fixed-ratio 1 (FR1) schedule by a lever-press on either the right or left lever. Both levers were presented initially and each lever-press resulted in a 4 s presentation of sucrose followed by retraction of that lever and presentation of the opposite lever. This procedure ensured that