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Differential effects of dopamine receptor subtype-specific agonists with respect to operant behavior maintained on a differential reinforcement of low-rate responding (DRL) schedule

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ABSTRACT

Previous studies have shown that d-amphetamine, a dopamine (DA) indirect agonist, alters operant responding with respect to the behavior maintained on a differential reinforcement of low-rate (DRL) schedule of reinforcement. These behavioral changes have been presumed to result from drug-induced hyperdopaminergia that leads to activation of DA receptors. This study investigated the acute dose effects of DA receptor subtype-selective agonists on the performance of DRL 10-sec behavior by rats. SKF38393 (a D1 receptor agonist) and quinpirole (a D2/D3 receptor agonist) were able to dose-dependently disrupt DRL 10-sec behavior by decreasing the total responses, the non-reinforced responses, and the peak rate of response. Bromocriptine (a D2/D3 receptor agonist) produced a significantly different pattern of behavioral changes when examined during two distinct time phases (15 min and 3 hr after the drug injection). DRL responding was only altered at higher doses of bromocriptine in the second phase as indicated by decreasing reinforced responses and peak rate, together with an increase of burst responses. In contrast to the D1 and D2/D3 receptor agonists, PD168077 (a D4 receptor agonist) did not affect DRL 10-sec behavior. None of these tested drugs affected DRL 10-sec behavior in a manner similar to that of d-amphetamine. These findings show that there are differential effects on the performance of DRL 10-sec behavior when drugs are able to preferentially activate D1, D2/D3 and D4 receptors, supporting the assertion that there is functional heterogeneity of the DA receptor subtypes.

1. Introduction

The central dopamine (DA) systems play an important role in the regulation of behavioral functioning, and perturbation of DA neurotransmission is known to cause the development of mental dysfunction and psychiatric disorder. Over the years subtypes of DA receptors have been categorized using biochemical and genetic approaches (Neve et al., 2004; Rankin et al., 2010). And, accumulating evidence supports the idea that two DA receptor families show heterogeneous functions based on both pharmacological and physiological approaches (Beaulieu and Gainetdinov, 2011; Jackson and Westlind-Danielsson, 1994; Missale et al., 1998), behavioral domain studies (Beninger et al., 1989; Floresco and Magyar, 2006; Joyce, 1983; Waddington et al., 1995), and associated psychiatric disorders (Lauzon and Laviolette, 2010; Seeman, 2013; Vallone et al., 2000). The D1-like family consists of the D1 and D5 receptors, while the D2-like family consists of the D2, D3, and D4 receptors. However, the exact role of these DA receptor subtypes in behavioral functioning in terms of reward motivation and/or cognitive processing is still a matter of debate. The effects of selective DA receptor agonists or antagonists have been tested using a variety of behavioral tasks developed on the basis of either classical or operant conditioning. Operant behavior maintained on a specific type of reinforcement schedules manifests distinctive behavioral characteristics (Ferster and Skinner, 1957) and this paradigm has been widely employed to assess or screen psychoactive drugs using animals as the subject material during preclinical studies (e.g. Hudzik et al., 2014; Sanger and Blackman, 1989). However, results have mostly been accumulated from studies involving the testing of DA receptor antagonists. There have been only a few reports on the effects of selective DA receptor agonists on schedule-controlled behavior in the operant psychopharmacology. A specific schedule of reinforcement called the differential reinforcement of low-rate responding (DRL) has received even less attention in the research of this topic.

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The DRL behavioral task was initially developed based on the idea of combining the response ratio and time interval of the operant paradigm. Compared to operant responding to other schedule-controlled behaviors, especially those based on a fixed-type schedule of reinforcement, the subjects performing the DRL task normally show a lower response rate (Kramer and Rilling, 1970). In addition, operant behavior maintained on the DRL schedule has been characterized as showing temporal regulation (Bayley et al., 1998; Cheng et al., 2006; Liao and Cheng, 2005; McClure and McMillan, 1997; Paule et al., 1999; Sanger and Blackman, 1975) as well as behavioral inhibition (Bardo et al., 2006; Monterosso and Ainslie, 1999; Neill, 1978; Peterson et al., 2003; Stoffel and Cunningham, 2008). Rats trained on this schedule of reinforcement are required to inhibit or withhold lever pressing for a minimum specified period of time (generally in a range from 5 to 72 seconds) in order to obtain a chance that the response results in the reinforcer being given. An early or premature response resets the program clock and then the subject has to wait again from the time a non-reinforced response is made. This reset or "penalty" distinguishes the DRL procedure from other schedules of reinforcement such as the fixed-ratio (FR) schedule which normally generates high-rate responding. Also, the DRL task is distinctive from other temporal discrimination tasks (e.g. the discrete-trial temporal bisection task) and temporal differentiation tasks (e.g. the peak procedure), in which no program clock reset is involved (Body et al., 2013; Buhushi and Meck, 2005; Killeen et al., 1997). It has been shown that a premature response made at a time very close to the criterion time is more likely to induce a follow-up burst responding, which is defined as responses within 2 sec from the previous response (Cheng et al., 2008). Burst responding is a unique measure in the DRL procedure and high burst responding is counterproductive because every premature response resets the clock and further delays the coming of the next potential reward. Thus, this measure can be considered as measuring emotional response or impulsivity when the rats fail to obtain the reward with early or premature response in the DRL procedure (Simon et al., 2013).

Substantial evidence shows that psychostimulant drugs are able to alter DRL behavioral responses (Liao, 2009). Despite this, it should be noted that the potentially dissociable drug effects have not been reported until recently as such studies implement sophisticated tools for data analysis. For instance, d-amphetamine produces a significant horizontal shift in the inter-response time (IRT) distribution to the left on DRL behavioral response as quantified by the decrease of peak time, corresponding to an increase in non-reinforced responses and a decrease in reinforced responses (Liao and Cheng, 2005). These results for d-amphetamine with respect to DRL responding are consistent with data from the other studies analyzed both qualitatively and quantitatively (Fowler et al., 2009; Richard et al., 1993). Furthermore, d-amphetamine induced behavioral changes in terms of DRL tasks are able to be partially reversed by selective D1 and D2 receptor antagonists, which suggests an underlying DA-dependent mechanism (Cheng and Liao, 2007). As a result, it has thus been postulated that the effects of d-amphetamine on DRL behavior are associated with the hyperdopaminergia and may involve the activation of dopamine receptors. No study, as yet, has attempted to verify the aforementioned hypothesis by conducting experiments with the injection of drugs directly and preferentially activating DA subtype receptors in rats maintained on the DRL schedule of reinforcement. Accordingly, the present study sought to evaluate the dose-response effects of D1, D2/D3, and D4 receptor agonists on the performance of DRL 10-sec behavior. SKF38393, a D1 receptor agonist, quinpirole and bromocriptine, D2/D3 receptor agonists, and PD168077, a D4 receptor agonist were used and the results were evaluated by both qualitative and quantitative analysis of the IRT data of DRL 10-sec behavior in a manner that paralleled the approach used previously for d-amphetamine (Cheng and Liao, 2007; Liao and Cheng, 2005).

2. Methods

2.1. Subjects

The subjects were male Wistar rats (BioLASCO Taiwan Co., Ltd), averaging approximately 250 g of body weight upon receipt. The rats were housed individually. After 10 days of adaptation to the food and water provided *ad libitum*, the rats were maintained on a water-restriction regimen such that there was 5 min access to tap water in the home cage occurring no sooner than 30 min after the end of each daily experimental session. The rats were monitored and kept at 85% of their pre-restriction body weight. Food pellets were continuously available in each home cage. Training and/or test sessions were conducted daily at the same time (10:00–15:00) each day during the light portion of the vivarium's 12/12-h light/dark cycle (light on at 7:30 a.m.). The temperature of the colony and the behavioral test room was maintained at 23 ± 1 °C throughout the experiment. All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by an institutional review committee.

2.2. Apparatus

Behavioral measures were conducted using a custom-made operant system with four chambers located in a room separate from the animal colony. The interior dimensions of each chamber were 20 × 25 × 30 cm (MED Associated, St. Albans, VT, USA). Aluminum panels formed the front and back walls, and clear Plexiglas comprised the remaining sides and the top. Stainless steel rods (with a diameter of 5 mm) were set 11 mm apart to provide flooring. Each chamber was equipped with a lever positioned 7.3 cm above the floor and 4 cm from the right corner of the front panel. A liquid dispenser was set outside of the front panel of the chamber. The reinforcer delivery mechanism gave 0.04 ml of tap water at each presentation. The water was delivered into a receiving dish (25 mm diameter) located at the center of the front panel and 2 cm above the floor. The chamber was illuminated by a small light bulb located 10 cm above the floor and positioned 5 cm from the left corner of the front panel. Each chamber was enclosed in a plywood box with a fan to provide the necessary ventilation and to mask any outside noise. The four operant chambers were serviced and controlled by a microcomputer with an in-house designed program to control the operant environment as well as to allow data collection (Cheng and Liao, 2007).

2.3. Drugs

All drugs, namely SKF38393 hydrochloride, quinpirole hydrochloride, bromocriptine mesylate, and PD168077 maleate, were obtained from Tocris Cookson (Bristol, UK). The drug solutions were freshly prepared before the behavioral tests. SKF38393, quinpirole, and bromocriptine were dissolved in normal physiological saline, whereas PD168077 maleate was dissolved in 2% dimethyl sulfoxide (DMSO) and normal saline. Doses of each drug were as follows: SKF38393 (0, 1, and 3 mg/kg), quinpirole (0, 0.01, and 0.03 mg/kg), bromocriptine (0, 1, 2, 4, 8, 16, and 32 mg/kg), and PD168077 (0, 0.5, 1.0, and 3.0 mg/kg). Doses and pretreatment times were referenced via a pilot study in this laboratory and via previous studies examining the effects of systemic injection of these drugs on the conditioned behaviors in the rat (Cory-Slechta et al., 1996; Knapp and Kornestsky, 1994; Koffarnus et al., 2009; Nayak and Cassaday, 2003; Sanger et al., 1996; Weissenborn et al., 1996). The doses used in this study were selected with to the aim of avoiding the appearance of any gross motor deficit or stereotypy behavior in the subject under drug treatment.