Neuropharmacology 87 (2014) 173–179

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Effects of amphetamine on delay discounting in rats depend upon the manner in which delay is varied

David R. Maguire [a], Cedric Henson [a], Charles P. France [a,b,*]

[a] Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[b] Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

ARTICLE INFO

Article history:
Available online 26 April 2014

Keywords:
Amphetamine
Delay discounting
Order of delay presentation
Lever press
Rat

ABSTRACT

Whether stimulant drugs like amphetamine increase or decrease choice of larger delayed reinforcers over smaller immediately available reinforcers under delay discounting procedures can depend on several factors, including the order in which delay is presented. This study examined whether the order of delay presentation impacts drug effects on discounting in rats ($n = 8$) trained and tested under an ascending order, a descending order, as well as under a fixed delay condition. Responses on one lever delivered 1 food pellet immediately and responses on the other lever delivered 3 food pellets immediately or after a delay (4–32 s). In Experiment 1, the delay to the larger reinforcer varied within session and the order of delay presentation (ascending or descending) varied across conditions. In Experiment 2, the same delay value was presented in all blocks of the session (i.e., delay was fixed), and delay varied across conditions. Under the ascending order of delay, amphetamine (0.32–1.78 mg/kg) increased choice of the larger reinforcer in some rats and decreased choice in others. In the same rats responding under the descending and fixed delay conditions, amphetamine markedly decreased choice of the larger reinforcer even in the component associated with no delay. In some subjects, the effects of amphetamine differed depending on the manner in which delay was presented, indicating that drug-induced changes in performance were due, in part, to mechanisms other than altered sensitivity to reinforcer delay. These results also suggest that a history of responding under both orders of delay presentation can modulate drug effects.

This article is part of the Special Issue entitled 'CNS Stimulants'.

1. Introduction

Delay discounting is a process whereby the effectiveness of a consequence decreases as a function of the delay to its presentation (Mazur, 1987). Delay discounting is thought to be an important behavioral process because of its apparent relevance to many socially important behavioral problems, particularly behavior that reflects greater impulsivity or a lack of self-control (Ainslie, 1974; Rachlin and Green, 1972; Logue, 1988; Evenden, 1999). For example, current drug abusers discount the value of delayed reinforcers more rapidly than former users or individuals that have never used drugs [see Bickel et al. (2012, 2014)]; enhanced discounting might predispose an individual to choose the more immediately available effects of drug taking rather than the delayed benefits of remaining abstinent such as health, income, and positive social interactions. Understanding processes that underlie such choices and knowledge of how certain experiences (e.g., drug use) further impact delay discounting will possibly aid in the development of more effective prevention and treatment strategies.

Many procedures have been developed to study how physiological, pharmacological, and behavioral factors impact delay discounting [for example, see Madden and Bickel (2010)], such as the procedure developed by Evenden and Ryan (1996) in which subjects choose between a small reinforcer (e.g., 1 food pellet) delivered immediately and a larger reinforcer (e.g., 3 food pellets) delivered immediately or following a delay. Delay to delivery of the larger reinforcer is varied systematically across blocks within the session with the most common variation of the procedure being one in which delay progressively increases across blocks (i.e., ascending delays). Delay functions obtained in this manner typically reflect a shift in preference from responding predominantly for the larger reinforcer early in the session, when the larger reinforcer is delivered immediately, to responding predominantly

* Corresponding author. Department of Pharmacology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA. Tel.: +1 210 567 6969; fax: +1 210 567 0104.
E-mail address: france@uthscsa.edu (C.P. France).

http://dx.doi.org/10.1016/j.neuropharm.2014.04.012
0028-3908/

for the smaller reinforcer later in the session, when delivery of the larger reinforcer is delayed. The ability to rapidly assess delay discounting within a single session for individual subjects after relatively few (<30) training sessions (e.g., Evenden and Ryan, 1996) is suitable for behavioral pharmacology because it allows for determination of discounting at specific time points (e.g., acute drug effects) as well as evaluation of changes in discounting across time (e.g., during chronic drug administration or after discontinuation of drug administration) [see reviews by Perry and Carroll (2008), de Wit and Mitchell (2010), and Bari and Robbins (2013)].

The benefits of changing environmental variables such as delay within-session can be accompanied by potentially important issues (e.g., order effects) that can be addressed empirically by employing different procedural variations (Sidman, 1960). For example, the effects of stimulant drugs such as amphetamine on delay discounting can differ qualitatively, either increasing or decreasing discounting, depending upon whether the delay period is paired with a unique stimulus (e.g., Cardinal et al., 2000). A recent study (Tanno et al., 2014) showed that the effects of amphetamine and methylphenidate on performance under a delay discounting procedure vary depending on the order in which delays are presented within the session. Both drugs increased choice of the larger delayed reinforcer in rats responding under an ascending order of delay, consistent with effects reported by others (e.g., Barbelivien et al., 2008; Cardinal et al., 2000; Huskinson et al., 2012; Pitts and McKinney, 2005; Slezak and Anderson, 2011; Slezak et al., 2013; van Gaalen et al., 2006; Winstanley et al., 2003, 2005), but markedly decreased choice of the larger reinforcer in a separate group of rats responding under a descending order. A similar study (Slezak and Anderson, 2009) examined the effects of amphetamine in rats trained and tested under both an ascending and a descending order of delay. Amphetamine decreased choice of the larger reinforcer under both orders of delay; however, the effects of amphetamine were more pronounced under the descending order, possibly reflecting an interaction with delay order within the same subject.

Taken together, the results of these studies raise the possibility that changes in performance under an ascending delay procedure are influenced by factors other than, or in addition to, changes in delay discounting. For example, stimulant drugs might increase perseveration, alter the estimation of the passage of time, or change sensitivity to reinforcer amount [see discussions by Pitts and Febbo (2004), Pitts and McKinney (2005), Richards et al. (1997), and Slezak and Anderson (2009)]. Because Tanno et al. (2014) assessed the interaction between drug effects and delay order using a between-groups design, differences might be due to factors other than, or in addition to, delay order; it might be the case that a history of responding exclusively with one order of delay enhances the apparent perseverative effects of amphetamine. One goal of the current study (Experiment 1) was to examine whether the delay-order effect reported previously could be demonstrated for an individual subject; therefore, the effects of amphetamine were assessed in rats that were trained and tested under both ascending and descending orders of delay presentation.

Studies using either a between-groups (Tanno et al., 2014) or within-subject (Slezak and Anderson, 2009) design failed to show that amphetamine increases choice of larger delayed reinforcers (e.g., reduces delay discounting) when delay is presented in a descending order within session. If drug effects are mediated through changes in sensitivity to reinforcer delay, then such changes should be evident under various other conditions in which delay impacts behavior. Some data support the notion that amphetamine reduces sensitivity to reinforcer delay (e.g., Ta et al., 2008); however, amphetamine also impacts other behavioral processes thought to be relevant to delay discounting such as sensitivity to reinforcer amount (Maguire et al., 2009). A second goal of the current study (Experiment 2) was to determine whether amphetamine increases choice of larger, delayed reinforcers under conditions in which the impact of the order of delay presentation is reduced. Thus, the delay to the larger reinforcer was held constant within and across sessions, and delay was varied systematically across conditions.

2. Materials and methods

2.1. Subjects

Eight experimentally naïve, adult male Sprague–Dawley rats (Harlan Sprague–Dawley, Inc., Indianapolis, IN), approximately 3 months old at the beginning of the experiment, were housed individually in 45 × 24 × 20 cm high plastic cages containing rodent bedding (Sani-chips, Harlan Teklad, Madison, WI) in a colony room maintained on a 14:10 light/dark cycle with lights on at 0630 h; experiments were conducted during the light period. Rats were fed chow (Rat Sterilizable Diet, Harlan Teklad) post-session to maintain their body weights at approximately 360 g. Water was available continuously in the home cage.

2.2. Apparatus

Sessions were conducted in sound-attenuating, ventilated enclosures (ENV-022M; Med Associates, Inc., St Albans, VT), which contained an operant conditioning chamber (ENV-008CT; Med Associates, Inc.) with an interior space measuring 31 × 24 × 21 cm high. The front door and rear panel were clear polycarbonate and both ends were aluminum panels. The right panel was equipped with two response levers horizontally aligned 11.5 cm apart, above each of which was a 2.5-cm diameter translucent circle that could be trans-illuminated white with a 100 mA light (lever lights). A 5 × 5 cm opening was centrally located between the two levers through which 45-mg food pellets (PJAI-0045; Noyes Precision Pellets, Research Diets Inc., New Brunswick, NJ) were delivered from a food hopper. The panel on the opposite side of the chamber was equipped with a 100 mA houselight centrally located near the top of the chamber. Data were collected using MED-PC IV software and a PC-compatible interface (Med Associates, Inc.).

2.3. Behavioral procedures

2.3.1. Initial training

Sessions began with illumination of the houselight and both lever lights; a response on either lever extinguished lever lights and delivered one food pellet immediately followed by re-illumination of the lever lights, signaling the next opportunity to respond. After 3 consecutive sessions in which 50 food pellets were delivered within 30 min, the number of food pellets available on the non-preferred lever, defined as the lever on which less than 50% of responses occurred for 3 consecutive sessions, increased to 3. After the first session in which at least 80% of responses occurred on the lever that delivered 3 pellets, the contingencies were reversed until at least 80% of responses occurred on the opposite lever. After at least 2 such alternations, the experimental procedure was introduced. The lever that delivered 3 food pellets was counterbalanced across rats and was maintained for an individual rat for the entire study.

2.3.2. Delay-discounting procedure

The behavioral procedure used in the current study was based on the procedure developed by Evenden and Ryan (1996) and recently described by Tanno et al. (2014). Daily sessions were divided into 5 blocks, each of which comprised 2 forced trials followed by 5 choice trials. The houselight was illuminated at the beginning of the block and remained illuminated for the duration of the block. Blocks were separated by a 30-s blackout period, during which all lights were extinguished. The beginning of a trial was signaled by illumination of one (forced trials) or both (choice trials) lever lights. A response on an active lever (i.e., located directly below an illuminated lever light) delivered either 1 food pellet immediately or 3 food pellets either immediately or after a delay of 4, 8, 16, or 32 s. When food was delivered immediately, lever lights were extinguished immediately upon the response. When food was delivered after a delay, lever lights were extinguished immediately upon the response and the light located above the lever associated with delayed food flashed at a rate of 1 Hz for the duration of the delay. If no response occurred within 20 s of the beginning of a trial (limited hold), lever lights were extinguished and the trial was recorded as an omission. Food delivery or an omission initiated an inter-trial blackout period during which the lever lights were extinguished. The duration of the inter-trial blackout period was adjusted for each trial such that trials started every 60 s.

2.4. Experiment 1: ascending versus descending order of delay presentation

The first experiment assessed the effects of amphetamine in rats trained and tested under both an ascending and a descending order of delay presentation. Initially, rats chose between 1 and 3 food pellets delivered immediately for all 5 blocks of the session (no-delay sessions). After rats responded reliably on the lever