Pharmacology, Biochemistry and Behavior 150–151 (2016) 31–38

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Effects of NMDA receptor antagonists on probability discounting depend on the order of probability presentation

Justin R. Yates *, Kerry A. Breitenstein, Benjamin T. Gunkel, Mallory N. Hughes, Anthony B. Johnson, Katherine K. Rogers, Sara M. Shape

Department of Psychological Science, Northern Kentucky University, USA

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 12 September 2016
Accepted 14 September 2016
Available online 15 September 2016

Keywords:
Risky decision making
Probability discounting
Glutamate
NMDA receptor
Rat

ABSTRACT

Risky decision making can be measured using a probability-discounting procedure, in which animals choose between a small, certain reinforcer and a large, uncertain reinforcer. Recent evidence has identified glutamate as a mediator of risky decision making, as blocking the *N*-methyl-D-aspartate (NMDA) receptor with MK-801 increases preference for a large, uncertain reinforcer. Because the order in which probabilities associated with the large reinforcer can modulate the effects of drugs on choice, the current study determined if NMDA receptor ligands alter probability discounting using ascending and descending schedules. Sixteen rats were trained in a probability-discounting procedure in which the odds against obtaining the large reinforcer increased (n = 8) or decreased (n = 8) across blocks of trials. Following behavioral training, rats received treatments of the NMDA receptor ligands MK-801 (uncompetitive antagonist; 0, 0.003, 0.01, or 0.03 mg/kg), ketamine (uncompetitive antagonist; 0, 1.0, 5.0, or 10.0 mg/kg), and ifenprodil (NR2B-selective non-competitive antagonist; 0, 1.0, 3.0, or 10.0 mg/kg). Results showed discounting was steeper (indicating increased risk aversion) for rats on an ascending schedule relative to rats on the descending schedule. Furthermore, the effects of MK-801, ketamine, and ifenprodil on discounting were dependent on the schedule used. Specifically, the highest dose of each drug decreased risk taking in rats in the descending schedule, but only MK-801 (0.03 mg/kg) increased risk taking in rats on an ascending schedule. These results show that probability presentation order modulates the effects of NMDA receptor ligands on risky decision making.

1. Introduction

In probability discounting, animals are allowed to choose between a small, certain reinforcer and a large, uncertain reinforcer. One of the most common tasks used to study probability discounting in animals is an adaptation of a delay-discounting procedure developed by Evenden and Ryan (1996). In this procedure, the probability of obtaining a large, uncertain reinforcer decreases across blocks of trials, whereas the probability of obtaining a small magnitude reinforcer remains constant. Animals will generally discount the large reinforcer as the probability of its delivery decreases (or alternatively, as the odds against its delivery increases; odds against = [1/probability] – 1; Rachlin et al., 1991). Consistently choosing the large, uncertain reinforcer is typically considered to reflect risky decision making, although it is important to note that this behavior is not always maladaptive. For example, consider a hypothetical situation in which an individual has a 100% chance of receiving $20 or a 50% chance of winning $100. According to expected utility theory, the expected outcomes of each choice are $20 and $50, respectively. In this case, choosing the probabilistic reinforcer is advantageous. Regardless, risky decision making is associated with attention deficit/hyperactivity disorder (ADHD; see Dekkers et al., 2016 for a meta-analysis), borderline personality disorder (Schuermann et al., 2011; Svaldi et al., 2012), human immunodeficiency virus (HIV; Fujiwara et al., 2015; Hardy et al., 2006), obsessive-compulsive disorder (OCD; Grassi et al., 2015), psychopathy (Takahashi et al., 2014), sleep deprivation (Killgore et al., 2006), substance abuse (Brevers et al., 2014; Schutter et al., 2011), and pathological gambling (PG; Brand et al., 2005; Madden et al., 2009). Directly related to probability discounting, individuals diagnosed with psychopathy and PG often show shallower discounting of a large, uncertain reinforcer relative to matched controls (Madden et al., 2009; Takahashi et al., 2014).

Recently, the glutamatergic system has been linked to several disorders, including ADHD (see Archer and Garcia, 2016 for a review), OCD (see Grados et al., 2015 for a review), drug addiction (see Kalivas, 2009 for a review), psychopathy (Bortolato et al., 2012), and PG (see Pettorruso et al., 2014 for a review). Glutamate is the major excitatory neurotransmitter in the mammalian brain and binds to metabotropic and ionotropic receptors (see Ozawa et al., 1998 for a review). Currently, only ionotropic glutamate receptors have been examined in a probability-discounting procedure. Although administration of CNQX, an α-

* Corresponding author at: Department of Psychological Science, Northern Kentucky University, 1 Nunn Drive, Highland Heights, KY 41099, USA.
E-mail address: yatesj1@nku.edu (J.R. Yates).

http://dx.doi.org/10.1016/j.pbb.2016.09.004
0091-3057/

amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, does not affect probability discounting, *N*-methyl-D-aspartate (NMDA) receptor uncompetitive antagonists produce differential effects. MK-801 increases risky decision making, whereas ketamine decreases sensitivity to reinforcer magnitude (i.e., decreases responding for the large, uncertain reinforcer when its delivery is certain) without altering the rate of discounting (Yates et al., 2015). Because previous work has shown that drug effects in a probability-discounting procedure are dependent on the order in which probabilities are presented (St. Onge et al., 2010), the goal of the present study was to determine if probability presentation order modulates the effects of NMDA receptor ligands on risky decision making. MK-801 and ketamine were tested because they exhibit differential effects in a probability-discounting task (Yates et al., 2015). In addition to testing MK-801 and ketamine, we wanted to include an NMDA receptor ligand that lacks the psychotomimetic effects observed with uncompetitive antagonists (Harder et al., 1998; Krystal et al., 1994). As such, we included ifenprodil, a non-competitive antagonist that targets NR2B-containing NMDA receptors (Perin-Dureau et al., 2002).

2. Methods

2.1. Subjects

A total of 16 experimentally naïve, male Sprague Dawley rats (225–250 g upon arrival to the lab; Harlan Industries, Indianapolis, IN) were used in the current experiment. They were acclimated to an animal housing room and handled for six days before testing began. The housing room was maintained on a 12:12-h cycle (lights on at 0630 h), and rats were tested in the light phase (approximately 1100–1500 h). Rats were individually housed in clear polypropylene cages (51 cm long × 26.5 cm wide × 32 cm high) with metal tops containing food and a water bottle. Rats were fed 10 g of food each day immediately following behavioral testing, but they had ad libitum access to water in their home cage. All experimental procedures were carried out according to the Current Guide for the Care and Use of Laboratory Animals (USPHS) under a protocol approved by the Northern Kentucky University Institutional Animal Care and Use Committee.

2.2. Drugs

All drugs were purchased from Sigma Aldrich (St. Louis, MO). (+)-MK-801 hydrogen maleate and (±)-ketamine hydrochloride were prepared in sterile 0.9% NaCl (saline). Ifenprodil (+)-tartrate salt was prepared in distilled water. The two highest doses of ifenprodil (3.0 and 10.0 mg/kg) were heated and stirred prior to each injection. Each drug was injected at room temperature in a volume of 1 ml/kg. The doses were calculated based on salt weight.

2.3. Apparatus

Eight operant-conditioning chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT) located inside sound attenuating chambers (ENV-018 M; MED Associates) were used. The front and back walls of the chambers were made of aluminum, while the side walls were made of Plexiglas. There was a recessed food tray (5 × 4.2 cm) located 2 cm above the floor in the bottom-center of the front wall. An infrared photobeam was used to record head entries into the food tray. A 28-V white stimulus light was located 6 cm above each response lever. A 28-V white house light was mounted in the center of the back wall of the chamber. A nosepoke aperture was located 2 cm above the floor in the bottom-center of the back wall (the aperture was never used in the current experiment). All responses and scheduled consequences were recorded and controlled by a computer interface. A computer controlled the experimental session using Med-IV software.

2.4. Procedure

2.4.1. Magazine training

Rats were given two days of magazine training, in which 45 mg food pellets (F0021 dustless precision pellet, Bio-Serv, Frenchtown, NJ) were non-contingently delivered into the food tray. A total of 20 pellets was delivered according to a variable-time 30-s schedule of reinforcement. Each session lasted 10 min.

2.4.2. Lever-press training

For two sessions, rats learned to respond on each lever according to a fixed ratio (FR) 1 schedule of reinforcement. Each session began with illumination of the house light. A head entry into the food tray resulted in presentation of one lever; each lever was presented pseudo-randomly, with no more than two consecutive presentations of the same lever. A response on either lever resulted in delivery of one food pellet. Following a response on either lever, the house light was extinguished, and the lever was retracted for 5 s. After 5 s, the house light was illuminated. Each session ended after a rat earned 40 reinforcers or after 30 min, whichever came first. Following two sessions of FR 1 training, rats received three additional lever-press training sessions, in which the FR requirement increased between sessions (FR 3, FR 5, and FR 10, respectively). Each rat earned all 40 pellets during each session, with the exception of the first FR 1 training session.

2.4.3. Magnitude discrimination

Rats were given five days of magnitude discrimination training. Each session consisted of 40 trials, and each trial lasted 30 s. Each trial began with illumination of the house light. A head entry into the food tray extended one of the levers (the order of presentation between the two levers was pseudo-random, with no more than two consecutive presentations of the same lever). Responses on one lever (FR 10) resulted in immediate delivery of one pellet, whereas responses on the other lever (FR 10) resulted in immediate delivery of four pellets (the lever associated with the large magnitude reinforcer was counterbalanced across rats). Following completion of the response requirement on either lever, the house light was extinguished, and the lever was retracted for the remainder of the trial. If the response requirement was not completed within 20 s, the trial was scored as an omission, and the house light was extinguished for the remainder of the trial.

2.4.4. Probability discounting

Each session consisted of five blocks of 18 trials. The stimuli used to signal the beginning of each trial differed across blocks of trials (first: house light; second: house light and left stimulus light; third: house light and right stimulus light; fourth: house light and both stimulus lights; fifth: both stimulus lights). The first eight trials in a block were forced-choice trials, in which only one lever was pseudo-randomly presented (no more than two consecutive presentations of the same lever). The remaining trials were free-choice trials, in which both levers were extended. Ten responses on one lever always resulted in immediate delivery of one food pellet, whereas ten responses on the other lever resulted in probabilistic delivery of four pellets. For half of the rats, the odds against delivery of the large magnitude reinforcer increased across blocks of trials (0, 3, 7, 15, 31; corresponding to probabilities of 100%, 25%, 12.5%, 6.25%, 3.13%). For half of the rats, the odds against delivery of the large magnitude reinforcer decreased across blocks of trials (31, 15, 7, 3, 0). Following responses on either lever (FR 10), the stimuli used to signal the beginning of each trial were extinguished, and the levers were retracted for the remainder of the trial. If the response requirement was not completed within 20 s, the trial was scored as an omission, and all stimuli were extinguished for the remainder of the trial. Each trial lasted 30 s, regardless of how the rat responded. For example, if a rat completed the response requirement within 5 s, it would receive the reinforcer, and then would wait 25 s before the start of the next trial. Each session lasted 45 min.