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Short report

Evaluation of rate-dependency and internal clock effects of D-amphetamine

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ABSTRACT

The impact of two doses of D-amphetamine on rats' peak-interval performance was evaluated at two different points of training: with minimum training, 20 sessions, and with extended training, 120 sessions. At both points of training, none of the doses changed the location of the peak time; however, both doses caused a significant increase in the standard deviation of the response distribution during peak trials. Both results are incompatible with some previous empirical results, and with timing accounts that assume that dopamine modulates the pacemaker rate, but are compatible with a rate-dependent effect.

1. Introduction

The impact that temporal properties of the environment have on behavior has been extensively studied in many species and with different operant tasks designed specifically to model the relationship between behavior and time (for a review, see Church, 2002). One of these tasks is the peak procedure (Catania, 1970), which consists of the mixture of (a) fixed interval (FI) trials, in which a reinforcer is delivered for the first response after some fixed time after stimulus onset, and (b) peak trials, in which no reinforcer is delivered, and the stimulus lasts at least three times the duration of the FI. The usual result is that in peak trials the response distribution across trial time is roughly Gaussian (but see below), with its peak – which is regarded as the organism's estimation of the time of reinforcement – near the expected time of reinforcement; the standard deviation of the response distribution is often regarded as the precision of that estimate.

One of the topics that have received much attention is the neuropharmacology that underlies timing behavior (Meck, 1996). Specifically, for timing theories based on the concept of an internal clock, the dopamine system has been considered to play an important role in the modulation of the rate at which the clock runs (pacemaker rate) (for a review, see Cheng et al., 2007), with dopamine agonists increasing the rate (Maricq et al., 1981), and dopamine antagonists decreasing it (Buhusi and Meck, 2002). In the peak procedure, an increase in the pacemaker rate would result in a leftward shift in the response time distribution (i.e. an earlier mean). If the only influence of dopamine agonists is to increase the pacemaker rate, the standard deviation of the response distribution should not be increased.

The result that response distribution is shifted following dopamine agonists administration is not always found (Bayley et al., 1998; Odum et al., 2002a,b), suggesting that the effects of dopamine on the peak time should undergo further study. Although it has been reported that D-amphetamine induces a higher level of dopamine release in the prefrontal cortex than methamphetamine (Shoblock et al., 2003), it is unlikely that the particular dopamine agonist employed is the variable that explains the discrepant results; for example, considering the studies that employ D-amphetamine, while some of them report the leftward displacement of the peak time (Abner et al., 2001; Eckerman et al., 1987; Kraemer et al., 1997), about the same number report no displacement (Bayley et al., 1998; Odum et al., 2002a,b; Balci et al., 2008). A similar picture emerges from the analysis of the studies that employ methamphetamine (left displacement (Maricq et al., 1981; Matell et al., 2006), no left displacement (Balci et al., 2008)). These facts, summed to the reports that both drugs have similar pharmacokinetics properties and induce an equivalent change of dopamine release in the striatum (Melega et al., 1995) and in the nucleus accumbens (Shoblock et al., 2003), allow us to consider that the strong contrast in the results of the different studies is related more to procedural details than to the exact drug employed. A possibility suggested recently to explain the inconsistent effect of dopamine agonists on peak time, is that the amount of experience with the peak procedure is an important variable. Specifically, it was found that when subjects have extensive experience on the peak-interval procedure, they are insensitive to methamphetamine administration, a manipulation that in less experienced subjects provokes a leftward change in peak time (Cheng et al., 2007). Although these results seemed to explain the discrepant effects

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found in the literature, a recent study reported a null effect of dopamine agonists on the peak time even when subjects had been trained for only 20 sessions (Balci et al., 2008).

While the pacemaker theory has largely dominated the literature, other explanations of the effects of dopamine agonists have been proposed as well. An important finding in the behavioral pharmacology area is that the schedule of reinforcement has an important role in the determination of the effects of drugs (for a review, see Sanger and Blackman, 1976). In concrete, what now is known as the rate-dependency hypothesis (Dews, 1958), proposes that the administration of dopamine agonists would increase low response rates, but would decrease high response rates. In the peak-interval procedure, where a differential response rate across time is typical, this would be observed as a flattening of the response distribution, with no change in peak time. Unlike the pacemaker theory, the rate-dependency effect implies an increase in the standard deviation of the response time distribution in the peak procedure, and no change in peak time.

Starting from the rate-dependency principle, Saulsgiver et al. (2006) argued that it could also explain the D-amphetamine-induced leftward shift of the response time distribution if the rate-dependent effect of dopamine agonists is stronger before the expected time of reinforcement, and weaker after. This effect could be due to the differential range of response rate that is normally found in the peak-interval performance: while in the ascending part of the response distribution the range of response rate is considerably large (from very low at the beginning of the trial, to very high at the peak time), in the descending part the range of response rate is shorter (from very high response rate at the peak time, to moderate response rate during the rest of the trial (Galtress and Kirkpatrick, 2009)).

With the additional assumption that as training advances, the range of response rate in the descending part of the response distribution gets larger (Balci et al., 2009), the amount of training effect reported by Cheng et al. (2007) could be explained by the rate-dependency effect found in the behavioral pharmacology literature; in the present experiment, we evaluated this possibility by training rats in a standard peak procedure. We administered two doses of D-amphetamine (0.5 mg/kg and 1.0 mg/kg) at two different points in training: minimum training (20 sessions), and extended training (120 sessions). D-Amphetamine and methamphetamine are indirect dopamine agonists, which also impact on other neurotransmission systems (for a review, see Seiden and Sabol, 1993). We decided to use D-amphetamine, because it affects the dopaminergic system in a more specific way than methamphetamine (Sabol et al., 1995). The doses selected for the present experiment are in the range of the doses employed in the studies that have reported a leftward shift in the peak time (Abner et al., 2001; Eckerman et al., 1987; Kraemer et al., 1997).

2. Method

2.1. Subjects

Subjects were fifteen male Wistar rats, approximately 10 weeks old at the beginning of the experiment. Their mean weight (±SEM) was 302.84 ± 5.81 g. They were food restricted until they reached 85% of their free-feeding weight. Then they were fed approximately 13 g of laboratory chow per day to maintain this weight during the experiment.

2.2. Apparatus

15 operant conditioning chambers (MED Associates, Inc., Model ENV 008-VP) were used. The presentation of stimuli and the collection of data were controlled by personal computers using the Medstate programming language (for a full description of apparatus, see Orduna et al., 2008).

2.3. Procedure

2.3.1. Peak procedure

A standard peak procedure was employed. Each session comprised 65 trials, from which 50 were FI 30 s, and 15 were peak trials with a variable duration, at least 90 s. The reinforcer was a 45 mg food pellet (Bioserv, product F0165). The intertrial interval was variable with a mean of 45 s; during it, the lever was present, but the discriminative stimulus (light over the lever) was turned off (for details, see Orduna et al., 2008).

2.3.2. Drug administration

D-Amphetamine (Sigma/RBI, Saint Louis, MO, USA), in doses of 1 mg/kg, 0.5 mg/kg and vehicle (0.9% saline), was administered to all subjects, in two conditions defined by the amount of training experienced (a) with minimum training (20 sessions) and (b) with extended training (120 sessions). Each injection day was followed by at least two testing days in which no drug was administered. The different doses were administered in a semirandomized order, in a constant volume of 1 ml/kg of body weight, and were injected via intraperitoneal 15 min before the beginning of the session. In each condition, each dose was applied twice, and the data from those 2 days were pooled for data analysis. Two randomly chosen baseline sessions were analyzed to serve as control sessions.

2.3.3. Data analysis

2.3.3.1. Timing behavior parameters. The number of responses in each 1 s bin was summed across all peak trials from a session. The analysis was performed on bins 1–90. The response frequency was converted to response rate, and the next Gaussian equation was fitted to the individual data from each session:

$$y = ae^{[-0.5((x-x_0)/b))^2]} \quad (1)$$

where x is time since trial onset (in s), and x_0, a, and b are free parameters expressing the peak time, the peak response rate, and the standard deviation, respectively. The Weber fraction was calculated as the ratio of the standard deviation to the peak time (b/x_0). These data were obtained for the pooled data under each drug dose. Anovas were performed to evaluate differences in peak time, standard deviation and Weber fraction, with dose (1 mg/kg, 0.5 mg/kg, vehicle and control sessions), and phase (minimum training or extended training) as within subjects factors. An alpha level of .05 was used in all statistical tests. Scheffe Post hoc Analyses were performed when appropriate.

2.3.3.2. D-Amphetamine rate dependency effects. This analysis was based on the analysis performed by Saulsgiver et al. (2006). Briefly, the performance on drug sessions was compared to the baseline sessions by generating scatterplots of the log response rate under drug (or saline) as a function of the log response rate in baseline sessions. A straight line was fitted to the scatterplot by regressing the response rate under drug against baseline performance. Separate fits were obtained for data before and after the expected reinforcement time in peak trials. Anovas were performed to evaluate the effect of dose, phase, and before/after reinforcement. The slope and intercept of the fitted line were considered indices of the rate dependency effect (for details, see Gonzalez and Byrd, 1977).

3. Results

Fig. 1a and b shows the group mean of the response distribution (response rate per 1 s bin) during the baseline sessions and the