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The effects of clinically relevant doses of amphetamine and methylphenidate on signal detection and DRL in rats

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ABSTRACT

Low dose amphetamine (AMPH) and methylphenidate (MPH, Ritalin®) are the most widely prescribed and most effective pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD). Certain low, clinically relevant doses of MPH improve sustained attention and working memory in normal rats, in contrast to higher doses that impair cognitive ability and induce locomotor activity. However, the effects of AMPH of MPH on sustained attention and behavioral inhibition remain poorly characterized. The present experiments examined the actions of AMPH (0.1 and 0.25 mg/kg) and MPH (0.5 and 1.0 mg/kg) in a rat model of 1) sustained attention, where signal and blank trials were interspersed randomly and occurred at unpredictable times, and 2) behavioral inhibition, using a differential reinforcement of low rate (DRL) schedule. In a signal detection paradigm, both 0.5 mg/kg and 1.0 mg/kg MPH and 0.25 mg/kg AMPH improve sustained attention, however neither AMPH nor MPH improve behavioral inhibition on DRL. Taken together with other recent studies, it appears that clinically-relevant doses of AMPH and MPH may preferentially improve attention-related behavior while having little effect on behavioral inhibition. These observations provide additional insight into the basic behavioral actions of low-dose psychostimulants and further suggest that the use of sustained attention tasks may be important in the development of novel pharmacological treatments for ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with a dysregulation of working memory, sustained attention, behavioral inhibition/impulsivity and hyperactivity. Conservative estimates suggest that 3–5% of both children and adults are affected (Solanto, 1998; Wilens et al., 2004). Low doses of psychostimulants, amphetamine (AMPH) and methylphenidate (MPH), comprise the most common and most effective pharmacotherapy for ADHD (Greenhill, 2001). In ADHD-affected individuals, low-dose stimulants reduce motor activity while improving performance in tests of working memory, sustained attention and impulsivity (Solanto, 1998). Interestingly, the cognitive enhancing and behavioral calming actions of low-dose psychostimulants are not limited to individuals with ADHD, but also extends to "healthy" human and animal subjects (A. F. Arnsten and Dudley, 2005; Kuczenski and Segal, 2002; Mehta et al., 2000; J. L. Rapoport et al., 1980; Vaidya et al., 1998). These actions contrast with those of higher doses, which produce pronounced cognitive impairments and locomotor activation (McGaughy and Sarter, 1995; Segal, 1975).

Recently, we demonstrated biphasic dose-dependent actions of MPH on working memory, with beneficial effects observed at low doses but not at modestly higher doses (i.e. 2.0 mg/kg oral vs. 8.0 mg/kg oral). In addition, we showed that a clinically relevant dose of intraperitoneally (IP)-administered MPH (0.5 mg/kg) improved sustained attention in a signal detection task in rats (Berridge et al., 2006). However, little is known regarding the dose-dependency of the effect on sustained attention and the degree to which this is observed with other psychostimulants.

In addition, less information about the actions of low-dose psychostimulants on measures of behavioral inhibition in healthy animals has been gathered. Differential Reinforcement of Low Rates (DRL) schedules of reinforcement have been proposed as an assay of impulsivity (Monterosso and Ainslie, 1999; D. B. Neill, 1976; D.B.

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Neill and Herndon, 1978; Peterson et al., 2003). This schedule reinforces responding if a certain amount of time has expired between responses (i.e., inter-response times (IRTs) exceed a certain value). DRL schedules test impulsivity because the participant must respond at certain times, and inhibit responding at other times. Seiden and colleagues have shown that both MPH and AMPH disrupt, rather than improve, DRL performance (Balcells-Olivero et al., 1998; Sabol et al., 1995; Seiden et al., 1979), although they tested doses that induce locomotor activity and produce sensitization, thereby limiting the relevance of their findings to the therapeutic actions of these drugs. In humans, deficient DRL performance of ADHD subjects has been observed in one study (McClure and Gordon, 1984) but not others (Avila et al., 2004; Daugherty and Quay, 1991). Nevertheless, DRL schedules may be a useful screening tool for the therapeutic actions of psychostimulants on impulsivity/behavioral inhibition in animals given its face validity, ease of implementation, and amenability for use with non-human animals. Moreover, the effects of low dose psychostimulants (cf. higher doses) on this widely used paradigm are not known.

The current studies were designed to provide a more complete description of the effects of low-dose psychostimulants on sustained attention, as demonstrated in Berridge et al. (2006), and to assess the degree to which this extends to other commonly used psychostimulants in the treatment of ADHD. A second goal of the current studies was to examine the same psychostimulants, demonstrated to improve sustained attention, in other paradigms posited to assess response inhibition.

While several rodent models of ADHD have been developed, the present experiments used a "normal" rat strain for several reasons. First, MPH and AMPH have been shown to improve performance in a number of paradigms for both ADHD-affected and non-affected individuals (see citations above). These improvements are perhaps most parsimoniously explained as cognitive-enhancing effects of these drugs on both affected and non-affected individuals, in contrast to "impairment-reducing" effects on individuals with ADHD and cognitive-enhancing effects on non-ADHD individuals. Thus, employing a "normal" rodent model would reveal potentially important effects applicable to both ADHD-affected and non-affected individuals. Secondly, the most common rat models of ADHD suffer from some limitations and interpretive concerns. For example, while substantial data on attention and impulse-control problems have been generated in studies using the Spontaneous Hypertensive Rat (SHR), debates remain surrounding issues of the proper control strain (e.g., the progenitor strain vs. a "normal" strain like the Sprague-Dawley, (Sagvolden et al., 2009)). A recent review concluded that predictive validity of the SHR strain in drug efficacy studies is highly dependent on the behavioral test used (Heal et al., 2008). It seems prudent, then, to construct a more complete understanding of MPH's and AMPH's actions on behavior in an outbred strain before proceeding to the SHR model (or other, even less validated model). Lastly, the research presented here seeks to uncover the influence of psychostimulants on attention and behavioral inhibition, rather than the ameliorative effects of psychostimulants on ADHD. The rationale for studying psychostimulants' effects on attention and inhibition is provided by the fact that they are widely prescribed for the treatment of ADHD.

2. Method

2.1. Subjects

Male Sprague-Dawley rats (Harlan, Madison, WI) were housed in pairs in polyethylene cages in colony room with a 12:12 h light/dark cycle. Upon arrival, rats were approximately 70 days old and weighed approximately 300 g each. They were weighed and handled daily and provided with food ad libitum for 7 days. Each rat was reduced to 85% of its ad libitum weight over the course of approximately 3 weeks. Each rat was then feed between 9 and 15 g of chow per day at least one hour after a day's session. According to growth curves provided by the breeder, Sprague-Dawley rats normal gain about 15 g per week, thus body weights were allowed to increase about 12–13 g per week (roughly 85%). All rats were weighed immediately prior to a day's injection or session, thus ensuring the correct drug dose. Water was freely available in the home cage. Care of rats was in accordance with University of Wisconsin-Madison animal care committee guidelines. One squad of experienced rats ($n = 8$), used in a previous experiment (Berridge et al., 2006), served in the Signal Detection experiment. Prior to the present experiments, this squad of rats had experienced a total of 118 sessions of signal detection: 44 baseline training sessions, 27 drug injection sessions (which provided the data for Berridge et al., 2006), and 47 drug-free, re-establishment of baseline sessions. In that previous study, rats received low doses of MPH (0.5 mg/kg) and AMPH (0.1 mg/kg), in a similar fashion described below. Briefly, injections were never given on consecutive days and the order of injections was random. Because each subject served as its own control and the lengthy drug-free period in between drug testing phases, the prior drug exposure did not likely influence the present drug testing results (e.g., sensitization). Drug testing began with the first group when the rats were approximately 9 months old. The second squad of rats ($n = 8$) used in the DRL experiment were 70 days old, 300 g, and experimentally naïve at the start of that experiment. Care was identical to that of the first group.

2.2. Drugs

D-amphetamine hemisulfate (AMPH, 0.1 mg/ml, 0.25 mg/ml) and Methylphenidate hydrochloride (MPH, 0.5 mg/ml, 1.0 mg/ml) were obtained from Sigma–Aldrich (St. Louis, MO, USA). They were measured as salt, dissolved in sterile saline and administered IP in a volume of 1.0 ml/kg. Doses of MPH were selected because they produce clinically relevant plasma concentrations in rats, lack locomotor-activating effects, and improve spatial working memory and sustained attention (Berridge et al., 2006; Kuczenski and Segal, 2001, 2002). Doses of AMPH were selected because their administration produces increases in prefrontal catecholamine efflux comparable to those observed with clinically relevant doses of MPH while lacking locomotor-activating effects (Berridge and Stalnaker, 2002). AMPH, in the range used here, also produces dose-dependent changes in consummatory, spontaneous and unconditioned behavior, learning, and drug discrimination (see Grilly and Loveland, 2001 for review).

2.3. Experimental chambers

Sessions were conducted in standard tall operant conditioning chambers (Med Associates, St. Alban, VT, model ENV-007, interior dimensions: 305 mm wide, 241 mm deep, and 292 mm high) made of sheet metal and plexi-glass and enclosed in ventilated chests. Fans provided some masking noise continuously throughout sessions. Two retractable levers (Med Associates model ENV-112CM, 48 mm wide × 19 mm deep) could be projected into the chamber on the right-side wall. A force of approximately 0.20 N was required to depress the levers and register a response. Spaced equally between the two levers was a feeder trough into which 45 mg sucrose pellets (reinforcers, Bio-Serv, Dustless Precision Pellets, #F0042) could be delivered. Above each trough was a row of three stimulus lights (red, yellow, and green LEDs, ~1 lux when illuminated, Med Associates model ENV-222M) and above them was a 28V houselight (Med Associates model ENV-215M). Experimental events were arranged and recorded via a personal computer in the same room as the chambers, running Med-PC for Windows Version IV (Med Associates, St. Alban, VT).

2.4. Lever-press training

All rats were initially trained to lever press during 9 daily, 30-min sessions, as described elsewhere (Andrzejewski et al., 2007). All rats were lever pressing by the end of training.

2.5. Experimental design

Rats received extensive training and when performance was judged stable drug testing was started. Drug testing did not start until all of the rats in an experiment met stability criteria. In addition, rats were habituated to the injection procedure by: 1) lightly restraining them, exposing their peritoneal area, and gently poking them with a capped syringe (for 5–10 sessions), and then 2) giving 3 separate vehicle injections (spaced at least 2 days apart) after stability criteria were met (data from these sessions were not used). All rats then went through drug testing. During this phase, rats received injections 30 min prior to the start of the session. Each rat experienced a different, randomized order of drug injections with the constraint that they receive all 5 doses (vehicle, 0.1 AMPH, 0.25 AMPH, 0.5 MPH, and 1.0 MPH) at least once before a dose was repeated. All rats received 2 rounds of drug injections, however each round was randomly determined. Drug testing occurred every other session; there was at least one "drug free" session between injection sessions. Means were computed over the course of all drug testing, differentiated by rat and condition, facilitating a repeated-measures statistical analysis. Drug free data were compared to that from vehicle sessions; the results were not statistically