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Attention enhancing effects of methylphenidate are age-dependent

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ABSTRACT

The psychostimulant methylphenidate (MPH, Ritalin®) is used to treat a variety of cognitive disorders. MPH is also popular among healthy individuals, including the elderly, for its ability to focus attention and improve concentration, but these effects have not been shown to be comparable between aged and adult subjects. Thus, we tested whether MPH would improve performance in sustained attention in both adult and aged rats. In addition, we tested the impact of visual distraction on performance in this task and the ability of MPH to mitigate the effects of distraction. Adult (6–12 months) and aged (18–22 months) male Sprague–Dawley rats were given oral MPH, and their cognitive and motor abilities were tested. Results suggest that while MPH improves task performance in adults; there is no improvement in the aged animals. These outcomes suggest that the use of MPH for cognitive enhancement in elderly individuals may be ineffective.

1. Introduction

The number of elderly individuals in the United States is growing rapidly. The U.S. census reports that the percentage of adults age 65 and older is projected to increase from 12% in 2004 to 21% by 2050 (U.S. Census Bureau, 2012). The demand for healthcare for this age group is likely to increase proportionally, as well as the incidence of age-related health conditions such as Alzheimer's disease and Parkinson's disease. However, before these pathological conditions develop, many people will experience a normal age-related decline in cognitive function (Carlson et al., 2009; Robbins et al., 1994). This condition is defined in the DSM-IV as "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age. Individuals with this condition may report problems remembering names or appointments or may experience difficulties in solving complex problems." (American Psychiatric Association, 2000). The off-label prescription of cognition-enhancing psychostimulants for individuals of this age group is increasing (Galynker et al., 1997; Hanlon et al., 2001). This trend necessitates further investigation of the safety and efficacy of such drugs for cognitive enhancement in aging individuals.

The prefrontal cortex and its modulatory catecholamine systems have been implicated in executive function, attention, and working memory (Arnsten et al., 1994; Berridge and Devilbiss, 2011). Human studies have shown that loss of attention capacity occurs with normal aging (McGaughy and Eichenbaum, 2002). Parasuraman and Giambra (1991) tested young, middle-aged, and elderly adults using a vigilance task, and they found that the elderly group was significantly impaired compared to the two younger groups. Another study compared two groups of healthy aged individuals (mean ages 67.9 and 77.5 years, respectively) to patients diagnosed with Alzheimer's dementia (mean age 70.5 years) in a visual search task designed to test spatial attention capacity. Results showed that the visual attention capacity of the elderly individuals declined steadily from early old age to advanced old age and became more severely limited in Alzheimer's dementia (Greenwood et al., 1997). These studies suggest that age-related cognitive decline observed in otherwise healthy individuals includes deficits in attention, and these deficits may precede more serious cognitive disorders such as dementia.

Animal studies provide further behavioral correlates to the symptoms seen in human age-related cognitive decline as well as a platform for evaluating the possible neurobiological underpinnings of this condition. Barense et al. (2002) found that aged rats (age 27–28 months) had impairments in attention flexibility similar to deficits seen in young adult (age 4–5 months) rats with neurotoxic lesions to the medial frontal cortex (homologous with primate prefrontal cortex). These age-related impairments in the frontal cortex were independent of age-related changes in hippocampal function, suggesting that the frontal cortex may be a specific target for the treatment of age-related cognitive decline (Barense et al., 2002). Muir et al. (1999) tested adult (10–11 months) and aged (23–24 months) rats in the 5-choice

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serial reaction time task. The aged rats were significantly impaired in accuracy on this task compared to the adult rats, suggesting a decline in visual attention capacity with old age.

Psychostimulant drugs such as methylphenidate (MPH) promote arousal and attention. At the cellular level MPH blocks reuptake of the catecholamine transmitters norepinephrine (NE) and dopamine (DA) thereby increasing catecholaminergic transmission in brain regions innervated by noradrenergic and dopaminergic fibers (Riddle et al., 2005). At low doses that yield clinically-relevant plasma concentrations of the drug, MPH substantially increases the extracellular concentrations of NE and DA in the prefrontal cortex, while only modestly increasing levels of these transmitters in areas outside the prefrontal cortex (Devilbiss and Berridge, 2008). Subsequent behavioral testing showed that these clinically-relevant doses of MPH enhance rodent performance on executive tasks that rely on prefrontal cortical function (Devilbiss and Berridge, 2008).

In the present studies we used a sustained attention task (described in Berridge et al., 2012), a modified version of the task that included visual distraction, and a test of locomotor activity to assess the effects of low-dose oral MPH in adult and aged rats. Previous studies in our laboratory indicate that low-dose oral MPH will improve adult animal performance on tests of attention, while higher doses will impair attention and increase locomotor activity. Based on these data, we hypothesized that low-dose oral MPH would also improve performance in healthy aged animals in these tests of attention.

2. Methods

2.1. Animals

Male Sprague–Dawley rats that were tested when they were adult (6–12 months) or aged (18–22 months) were housed in plastic cages in a controlled environment on a 12 h/12 h light/dark cycle (lights on at 07:00). Subjects had access to food ad libitum but were restricted in their water intake so they maintained approximately 90% of their free-feeding body weight over the course of the experiment. All procedures have been approved by Drexel University College of Medicine's Institutional Animal Care and Use Committee and follow NIH guidelines.

2.2. Experimental design

The initial plan was for 10 rats to be tested as adults and later as aged animals in three behavioral experiments: sustained attention, visual distractor, and locomotor activity. With attrition, only 6 of the 10 were tested as aged subjects. Power analysis of the VI difference score outcomes were calculated at the peak effect of the drug in adult animals. Using an effect size of 0.05 for the minimum difference in VI score between groups and an observed standard deviation of 0.03 within groups, to achieve robust results with 80% power at an alpha level of 0.05, we calculated the minimum sample size to be $n = 6$, using the standard formula for sample size estimation with two means (Suresh and Chandrashekara, 2012). Similar power analysis was performed for the locomotor outcomes that produced the same result. All behavioral testing was performed between 13:00 and 17:00.

2.3. Drug preparation, dosing and delivery

MPH was delivered by oral administration, i.e. dissolved in saline and soaked into a piece of cereal (Frosted Cheerios®) in a volume of 1 ml/kg that was fed to the rat. For all experiments, oral MPH or saline was administered 15 min prior to behavioral testing. The drug was tested over a range of doses (2.0–12.0 mg/kg). Previous studies have shown that an oral dose range of 6.0 to 8.0 mg/kg MPH produces peak responses in sustained attention and attention set shifting tasks (Agster et al., 2011; Berridge and Devilbiss, 2011; Berridge et al., 2012). Likewise, this dose range of MPH results in clinically relevant plasma concentrations (Arnsten and Dudley, 2005; Berridge and Devilbiss, 2011; Wargin et al., 1983). Controls were fed a saline-soaked piece of cereal. Moistened cereal pieces were administered in a cage without bedding and in all cases full ingestion was observed. MPH HCL was purchased from Sigma-Aldrich, and diluted to a 5 mM stock solution in physiological saline. Prepared solution was stored at −20 °C in 1 ml aliquots.

2.4. Behavioral testing

2.4.1. Sustained attention task

Animals were trained in operant boxes (Med Associates, St. Albans, VT) consisting of a testing chamber encased within a sound and light attenuated outer wood casing. The testing chamber contains a house light (2.8 W), a stimulus light (2.8 W) and a pair of retractable levers all mounted on a front wall. A water delivery system is mounted to the opposing wall to the rear of the subject. Subjects can acquire 40 μl of water following correct lever responses by drinking from a cup extended by an external arm in the chamber. Stimulus light, house light, lever presentations, and water delivery are all controlled using MED-PC software (Med Associates, St. Albans, VT), which also collects performance data.

Animals were habituated to the operant chambers and the animal handler during initial water restriction. Initially, animals were taught to associate lever pressing with water reinforcement. Next, a stimulus light was randomly presented within a 15 second window prior to lever presentation. Responding after signal presentation on one lever was paired with water reinforcement. Responding on the other lever when the signal is not presented was also paired with water reinforcement. There were five possible outcomes for each trial: 1) "hit" — signal light presented, rat presses appropriate lever, reward; 2) "miss" — signal light presented, rat presses incorrect lever, no reward; 3) "correct rejection" — signal light is not presented, rat presses appropriate lever, reward; 4) "false alarm" — signal light is not presented, rat presses incorrect lever, no reward; 5) "omission" — rat fails to press any lever regardless of signal presentation, no reward. Vigilance Index (VI) is a quantitative measure of performance in the sustained attention task based upon signal detection theory and is calculated using the formula $VI = (\text{hits} - \text{false alarms}) / [2^*(\text{hits} \pm \text{false alarms}) - (\text{hits} \pm \text{false alarms})^2]$. Please see the paper by McGaughy and Sarter (1995) for a validation of the formula. Animals were trained to >59% correct responding to both signal (S) and non-signal (NS) presentations, with less than 25% omissions (Berridge et al., 2012; McGaughy and Sarter, 1995), which resulted in VI > 0.35 and indicates performance significantly above chance. Stimulus duration was 15 ms upon attainment of criterion performance. We have determined that the short stimulus duration of this training regimen pushes the animal to its perceptual threshold, thus maximizing the requirement for sustained attention in order to meet performance criteria. All sessions were 46 min with the initial minute providing acclimation to the chamber.

Once stable criterion performance was achieved, subjects began pharmacologic testing. To determine peak responding, we performed a dose response curve from doses of 2.0 to 12.0 mg/kg orally-administered MPH in both the adult and aged rats. A minimum washout period of 48 h was provided between drug administrations, after which baseline behavioral performance was measured again. In previous studies, we have not observed any evidence of drug sensitization or tolerance after 24 h between drug administrations (unpublished results).

2.4.2. Visual distraction

Following this dose response regimen in the standard sustained attention task, we re-established baseline performance for all animals and then introduced visual distraction to the task by flashing the house light at 0.5 Hz for the duration of the testing session. VI score was assessed on separate days following saline administration and 8.0 mg/kg oral MPH administration in this distraction condition in both the aged and adult rats.