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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 use of MPH for cognitive enhancement in elderly individuals may be ineffective.

Keywords

aging; attention; methylphenidate; monoamine; psychostimulant; rat

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

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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 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 12h/12h 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 Chandrashekhara, 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 minutes 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 $VI = (hits - false\ alarms) / [2 * (hits + false\ alarms) - (hits + false\ alarms)^2]$. 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 milliseconds 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 minutes 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 hours 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 hours between drug administrations (unpublished results).

2.4.2. Visual Distraction—Following this dose response regimen in the standard sustained attention task, we reestablished 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 8.0mg/kg oral MPH administration in this distraction condition in both the aged and adult rats.

2.4.3. Locomotor Activity—Our next goal was to determine whether there are any changes in the “therapeutic window” separating attention enhancing effects from motor side effects in adult vs aged animals. In the weeks following the collection of sustained attention performance data, locomotor activity was assessed in the same group of animals using the same doses of oral MPH that were examined in the sustained attention task. Following baseline testing and testing with an injection of saline, a dose response curve from doses of 2.0 to 12.0 mg/kg orally-administered MPH was constructed for both the adult and aged rats. A minimum washout period of 48 hours was provided between drug administrations. Rats were tested individually in 5 minute sessions in a Plexiglas open field box (Kinder Scientific) which measured 16 “ long x 16” wide x 12” deep. Infrared photobeams situated at 2” and 4” from the floor measured activity by recording the number of times the animal crossed one of these beams; these data were then sent to the MotorMonitor software program (Kinder Scientific) for further analysis. Locomotor activity was defined as the number of photobeam crossings produced by each rat during the test session, including the sum of horizontal, vertical and repetitive movements. The average locomotor activity score collected over 5 min for a rat that had received saline was 1400, which we have validated as reproducible and of sufficient range to measure significant drug-related changes.

2.5. Data analysis

Dose-response relationships in the sustained attention task, the visual distraction task, and the locomotor task were measured by the change in score compared to baseline for each animal except where otherwise noted. This approach eliminates a substantial amount of individual variability between subjects and allows for a more accurate assessment of drug effects. Behavioral data from both the sustained attention and locomotor experiments were analyzed using a two-way mixed model ANOVA, with MPH dose taken as a repeated measure, comparing adult ($n = 10$) and aged ($n = 6$) animals from the same initial group of 10 rats. *A priori* comparisons were planned to be performed at the peak effects of the drug. Because attrition occurred as the animals aged, a separate analysis was performed at doses that had produced positive effects comparing the same rats ($n = 6$) as adults and later as aged animals using a paired samples t-test (two-tailed). Sustained attention experiments with visual distraction were analyzed for the effect of distraction on baseline performance, as well as the effect of MPH on performance under distraction conditions. Both of these analyses used repeated measures ANOVA. Post hoc analyses were performed using one-way ANOVA or t-tests to assess significant differences among specific doses and ages as appropriate. Alpha levels were set at 0.05 for all comparisons. All data are presented as mean $\pm$ SEM.

3. Results

3.1 Sustained attention

No significant differences in baseline performance were found between the adult and aged animals (adult: $VI = 0.69 \pm 0.03$, aged: $VI = 0.74 \pm 0.08$), indicating that the aged rats maintained a similar capacity for performing the task as adult rats. Presented as the difference in VI from each animal's average baseline, the dose-response curves for the adult and aged Sprague-Dawley rats in the sustained attention task are shown in Figure 1. A two-way (age x MPH dose) mixed model ANOVA revealed a main effect for age [$F(1,9) = 4.67$, $p < 0.05$] and a main effect for treatment [$F(1,9) = 2.62$, $p < 0.05$] and no interaction. Post-hoc analyses of the main effects within each age group indicated that at doses of 6.0 mg/kg and 8.0 mg/kg oral MPH, the adult rats demonstrated a significant increase in VI score ($p < 0.05$). As a group the aged rats, however, did not exhibit a significant change from baseline performance at any dose of oral MPH.

A high degree of variability was observed in the aged sample, and further examination of the raw data revealed that this variability was largely the result of variable drug response between individuals. Two of the six aged rats retained some responsiveness to oral MPH (one at a lower dose and one a higher dose than their previous peak dose of 8 mg/kg), thus accounting for the high variability in this group. Similar inconsistency within aged populations has been noted in other behavioral studies of cognitive function (LaSarge and Nicolle, 2009).

The change in drug response for the subset of adult rats that survived to be tested as aged rats was analyzed with a paired samples t-test, and results are shown in Figure 2. All six adult rats demonstrated significant enhancement of VI score at a dose of 8.0mg/kg oral MPH ($t = 3.42$, $p < 0.01$). None of the six animals retained a measure of responsiveness to MPH when tested as aged rats at the dose of 8.0 mg/kg. Furthermore, when considered as a group, the effect of MPH was no longer evident at an advanced age.

3.2 Visual Distraction Task

The effects of visual distraction on baseline sustained attention performance are shown in Figure 3. A repeated measures ANOVA confirmed an effect of task type [$F(1,5) = 321.8$, $p < 0.001$]. A paired-samples t-test further showed that the presence of a visual distractor significantly impaired VI score to a similar degree in both the aged ($t = 14.07$, $p < 0.001$) and adult animals ($t = 11.3$, $p < 0.001$), with no differences in performance between the two age groups. Figure 4 shows the effects of 8.0mg/kg oral MPH on VI score for both groups in the presence of visual distraction. A repeated measures ANOVA revealed a main effect for treatment [$F(1,5) = 8.84$, $p < 0.01$] and no interaction with age. This analysis was followed by paired-samples t-tests that indicated that MPH significantly increases VI score in adult animals, partially ameliorating the deficit induced by the visual distraction ($t = 2.52$, $p < 0.05$). However, the aged animals showed no significant change from baseline performance in response to MPH.

3.3 Locomotor Activity

The dose-response curve for locomotor activity in adult ($n = 10$) versus aged ($n = 6$) Sprague-Dawley rats is shown in Figure 5. A repeated measures ANOVA revealed an interaction between MPH dose and age [$F(1,19) = 3.98$, $p < 0.05$]. Post hoc analysis confirmed a significant increase in the locomotor activity of adult rats at higher doses of oral MPH, with a peak in activity at 10mg/kg ($t = 2.35$, $p < 0.05$). By contrast, aged animals did not exhibit any significant change from baseline locomotor activity at any dose of oral MPH. A subsequent paired-samples t-test on the same group of animals ($n = 6$) tested as adults and then later as aged subjects produced the same results.

4. Discussion

These studies demonstrate that low-dose oral MPH is effective in enhancing vigilance in normal adult Sprague-Dawley rats, which corresponds to previous findings from our own laboratory as well as others in the field (Berridge and Devilbiss, 2011; Berridge et al., 2012). Our results indicate that while aged animals are still capable of performing the sustained attention task with an equivalent degree of proficiency as the adult rats, the beneficial effects of MPH treatment on vigilance are diminished in old age. By contrast, Glock et al (1977) reported that subcutaneous MPH improved avoidance learning in aged rats. The addition of a visual distractor to the sustained attention task significantly impaired performance to a similar degree in both adult and aged rats, but oral MPH administration was only capable of partially ameliorating this deficit in the adult rats. In addition, MPH did cause dose-dependent changes in locomotor activity in the adult rats, but aged rats showed no significant locomotor response to the drug at any dose.

Psychostimulant drugs are commonly used to treat cognitive deficits and behavioral problems in children and adults, including attention-deficit disorder (ADD), attention-deficit/hyperactivity disorder (ADHD), and sleep disorders such as narcolepsy. Recent studies in healthy adult volunteers have shown that MPH significantly occupies NET and DAT *in vivo* at clinically relevant doses, indicating the potential for the enhancement of attention and cognition in healthy individuals as well as those with ADHD (Hannestad et al., 2010). Such findings confirm that neither the biochemical actions of MPH nor the therapeutic cognitive effects of MPH are dependent on prefrontal catecholaminergic pathology, which supports the notion that MPH could potentially improve cognition in normal, healthy subjects. The use of MPH for improving academic performance is already widespread among students on college campuses (McCabe et al., 2005). However, the question remains as to whether such compounds might be appropriate for the treatment of age-related cognitive decline in otherwise healthy elderly individuals. MPH is already prescribed for elderly individuals with ADHD, treatment-resistant depression and apathy with mixed results (Hardy, 2009; Kerr et al., 2012; Manor et al, 2011; Padala et al., 2010; Patkar et al., 2006). Its efficacy for cognitive enhancement in this age group has not been clearly established. The results of our animal study provide evidence that MPH would not be effective as a cognitive enhancer in the aging human population.

A variety of factors may influence the efficacy of oral MPH in aged rats, including age-related changes in drug pharmacokinetics (absorption or metabolism) that would impact the

ideal dosage. MPH undergoes presystemic metabolism, primarily in the intestinal wall, to ritalinic acid, which is centrally inactive (Ding et al., 2004). Results from our laboratory and elsewhere (Berridge and Devilbiss, 2011; Berridge et al, 2012) indicate that oral doses of MPH between 6–8.0 mg/kg in adult animals achieve blood plasma levels in the range effective for ADHD treatment and also improve performance of normal rats in tests of working memory, sustained, and flexible attention. In the present study we tested a range of doses above and below the target doses of 6.0 and 8.0 mg/kg and conclude that oral MPH is ineffective in promoting vigilance in aged rats regardless of dose. Furthermore, although the inability of MPH to increase locomotor activity in aged animals argues in favor of a pharmacokinetic deficiency in this age group, the fact that some aged animals responded to MPH in the sustained attention test suggests the drug can act centrally in these animals. MPH enantiomers are known to have differential actions (Ding et al., 2004), and changes in metabolism with age could affect the racemic distribution of MPH. Nevertheless, an important consideration for future studies is determination of brain tissue levels of MPH following oral administration of the drug.

Some studies have linked low serum iron levels with the severity of ADHD symptoms in children (Konofal et al., 2008), and iron deficiency does commonly occur in elderly humans (Salive et al., 1992) and aged rats (Ahluwalia et al., 2000). While the rats used here were not tested for iron deficiency, more recent work has found no significant relationship between serum iron levels and ADHD symptomology (Donfrancesco et al., 2012).

An additional explanation for the failure of MPH to improve performance of aged animals in the sustained attention task might be tolerance to drug effects resulting from prior exposure of the animals to MPH as adults. However, in other studies conducted in our laboratory we have found no evidence of tolerance as a result of repeated MPH exposure. We have concluded that the most likely explanation and our working hypothesis for the lack of effect of oral MPH on vigilance performance in aged rats lies within the brain itself. MPH acts as a NE and DA reuptake inhibitor, increasing the availability of these neurotransmitters in several brain regions that modulate attention, including the prefrontal cortex. It is believed that the increased concentration of either or both of these two neurotransmitters in the prefrontal cortex is responsible for the enhanced attention observed in human subjects in response to MPH administration (Agster et al., 2011; Berridge and Devilbiss, 2011). Anatomical studies suggest that noradrenergic projections from the locus coeruleus to several areas of the brain, including the prefrontal cortex, decline with normal aging (Grudzien et al., 2007; Ishida et al., 2001a; Ishida et al., 2001b; Matsunaga et al., 2004), which would impact the ability of MPH to have the desired effect in these areas. Studies investigating the role of NE in motor learning in the cerebellum of aged rats have shown that aged animals are impaired in motor learning and that this impairment is related to a depletion of NE in the cerebellum (Bickford, 1993; Bickford et al., 1992). Taken together, these results suggest an age-related decline in NE function throughout the brain may be related to the cognitive decline observed in normal aging.

Research has shown that fewer viable noradrenergic neurons are present in the prefrontal cortex in aged versus adult rats (Ishida et al., 2001b), and thus the ability of MPH to enhance NE neurotransmission may be compromised. However, there are other aspects of the

noradrenergic system that may be altered with normal aging and may impact the efficacy of psychostimulant drugs such as MPH. For example, it is reasonable to suggest that the expression of noradrenergic receptors in neuronal membranes changes with age thus affecting the capacity for MPH to influence the operation of the prefrontal cortical circuitry. Likewise, recent developmental studies have shown that levels of cortical NET, a primary target of MPH, are much higher in juvenile rats than adults (Cain et al., 2011). This finding introduces the possibility that expression of NET may vary across the aging spectrum, potentially including old age. Future studies should focus on the fundamental anatomy of the prefrontal cortex in aged vs adult rats, specifically measuring the relative expression of NET, α_1 , α_2 , and β receptors within this area as well as evaluating the density and distribution of noradrenergic fibers and varicosities as release points for endogenous NE. Such data may provide insight as to why MPH fails to enhance various dimensions of cognitive function in aged subjects.

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Highlights

- We demonstrate that methylphenidate no longer improves attention in aged rats as it did when they were tested as adults.
- In addition, methylphenidate no longer enhances locomotor activity in aged rats as it did when they were tested as adults.
- We interpret this as possibly due to noradrenergic decline with aging.

Figure 1.

Dose-response curve for oral MPH in the sustained attention task in adult and aged male Sprague-Dawley rats. Adult rats increased VI scores in response to 6.0 and 8.0mg/kg oral MPH (* $p < 0.05$). Aged rats showed no significant effect of oral MPH on performance at any dose tested.

Figure 2.

The effect of 8.0mg/kg oral MPH on the same cohort of 6 rats tested at 3–6 months (adult) and 18–22 months (aged). While these rats responded to a dose of 8.0mg/kg oral MPH as adults with a significant increase in VI score (* $p < 0.01$), the same rats no longer respond to this dose at advanced age.

Figure 3.

The effect of visual distraction on baseline sustained attention performance in adult and aged rats. Both groups demonstrated significantly decreased VI in response to a visual distraction during the sustained attention task (* $p < 0.01$). The two age groups did not differ significantly in their baseline VI scores or their VI scores in the presence of distraction.

Figure 4.

The effect of 8.0mg/kg oral MPH on VI score in the presence of a visual distraction for adult and aged rats. Adult rats demonstrated a significant increase in VI score in response to MPH, partially ameliorating the deficit caused by the visual distraction (* $p < 0.05$, compared to baseline). By contrast, aged rats did not exhibit any enhancement in VI score as a result of MPH administration.

Figure 5.

Dose-response curve for the effects of oral MPH on locomotor activity in adult and aged rats. Adult rats showed a dose-dependent increase in locomotor activity with maximum activity at 10mg/kg oral MPH (* $p < 0.01$). Aged rats, however, did not experience any significant change from baseline at any dose of MPH, despite having done so as adults.