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Effects of memantine and galantamine on cognitive performance in aged rhesus macaques

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ABSTRACT

Current pharmacotherapies for Alzheimer's disease (AD) are focused on improving performance of daily activities, personal care, and management of problematic behaviors. Both memantine, a noncompetitive N-methyl-D-aspartate channel blocker and galantamine, a selective acetylcholinesterase inhibitor, are currently prescribed as symptomatic therapies for AD. However, drugs that progressed directly from testing in rodent models to testing in AD patients in clinical trials failed to demonstrate consistent effects on cognitive symptoms. Considering the lack of nonhuman primate data on the effects of memantine and galantamine alone or in combination on cognitive dysfunction in aged nonhuman primates, the present study examined how closely data derived from aged nonhuman primates reflects data obtained in humans. Mild beneficial effects on aspects of cognitive performance in aged primates were found, in general agreement with the human clinical experience with these drugs but in contrast to the more positive effects reported in the rodent literature. These data suggest that the nonhuman primate might have more predictive validity for drug development in this area than comparable rodent assays.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder affecting over 5 million Americans (Mebane-Sims, 2009) and over 26 million persons worldwide (Brookmeyer et al., 2007), with age and family history of the disease in a first-degree relative being the strongest epidemiological risk factors for AD (Sloane et al., 2002). The number of persons with AD is expected to increase over the next decades as the number of individuals worldwide older than the age of 60 years increases and thus the number of persons worldwide with AD can be expected to rise correspondingly, with estimates as high as almost 13 million persons in the United States suffering from AD by the year 2050 (Sloane et al., 2002). Although it is difficult to estimate the prevalence of age-related cognitive impairment or mild cognitive impairment because of inconsistencies in diagnostic criteria used in the literature (Bischkopf et al., 2002), the prevalence of age-related cognitive decline is estimated to be at least 20% in individuals older than 65 years of age (e.g., Rodríguez-Sánchez et al., 2011).

No drugs have been developed that can retard the progression of AD or prevent its occurrence and thus current pharmacotherapies are focused on improving performance of daily activities, personal care and the management of problematic behaviors (Sloane et al., 2002). Although cholinesterase inhibitors were the first drugs used to treat AD, there has been increasing evidence that targeting the glutamatergic system might be an effective therapeutic approach. Glutamatergic N-methyl-D-aspartate (NMDA) receptors are thought to play an important role in the pathology of AD (Wenk, 2006; Lipton, 2007) and are known to play important roles in memory processes (Shimizu et al., 2000). Overactivity in glutamatergic neurotransmission is believed to underlie at least some of the clinical manifestations of AD and thus, there has been an interest in the use of memantine, an uncompetitive NMDA-receptor antagonist, to treat AD patients (Danysz et al., 2000). Memantine was initially evaluated in moderate to severe AD patients, in whom positive effects were observed in some studies on measures of activities of daily living (Reisberg et al., 2003; Winblad et al., 2007) but in whom demonstration of positive effects on cognitive outcomes has been elusive (van Marum, 2009). Although memantine is indicated for moderate to severe AD, it is frequently also

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used in cases of mild AD and mild cognitive impairment (Schneider et al., 2011). However, a meta-analysis of available data on the use of memantine in mild to moderate AD found that there were indeed no significant differences between memantine and placebo on any outcome measures, including activity of daily living and cognitive measures (Schneider et al., 2011).

Considering the modest effects obtained with cholinesterase inhibitors and the disappointing results obtained with memantine, it has been suggested that particularly for mild to moderate AD, better results might be achieved with combination therapy with memantine and a cholinesterase inhibitor (Grossberg et al., 2006; Schneider et al., 2011). Galantamine is a selective and rapidly-reversible cholinesterase inhibitor that also acts as an allosterically potentiating ligand of neuronal nicotinic receptors (Ago et al., 2011). Combination therapy using galantamine and memantine has been suggested as a treatment for mild to moderate AD, with the possibility of having additive or synergistic effects by inhibiting acetylcholinesterase activity, inhibiting glutamatergic neurotransmission, and allosterically modifying nicotininc cholinergic neurotransmission simultaneously (Grossberg et al., 2006). Though this is a reasonable hypothesis, there have been no preclinical studies performed to evaluate whether such a combination therapy would have any better effect, particularly on cognitive outcomes, than either drug alone.

There is no good large animal model of AD currently available and thus, the bulk of preclinical drug development for AD has relied mostly on transgenic mouse studies or studies in aged rodents (Savonenko et al., 2012). The aged nonhuman primate, in which there are naturally occurring cognitive impairments, might be a useful model in which to assess therapies for cognitive enhancement. The aged nonhuman primate is an ideal model of age-related neurodegeneration in humans, because their behavioral repertoire closely resembles that produced by the human neurobehavioral system. Monkeys, like humans, develop age-related cognitive impairments in a variety of cognitive domains including memory and executive functioning as early as in middle age. Although monkeys do not naturally develop AD per se, they do develop substantial cortical and subcortical structural and neurochemical changes accompanied by a wide range of behavioral deficits (Hoff et al., 2002). As such these animals present a good model in which to assess potential therapies that might hold promise for improving cognitive dysfunction in age-related diseases such as mild cognitive impairment or early and mild AD.

Although a number of studies have reported positive effects of memantine or galantamine in aged rodents (Hernandez et al., 2006; Pieta Dias et al., 2007) or rodent models of AD (Martinez-Coria et al., 2010; Minkeviciene et al., 2004; Van Dam et al., 2005), there is a lack of data on the effects of memantine and galantamine alone or in combination on cognitive dysfunction in aged nonhuman primates. Thus, the present study was conducted to examine how closely data derived from aged nonhuman primates might reflect data obtained with these drugs in mild AD patients and examine the extent to which this model could be used to predict whether combination therapy with memantine and galantamine would produce better effects on cognitive functioning than either drug administered individually.

2. Methods

2.1. Animals

The study was conducted using 7 male Rhesus macaques (*Macaca mulatta*, Xierxin, China; age ranging between 23 to 26 years) previously trained to perform cognitive tasks (6 performed delayed matching to sample and 7 performed paired associate learning) and previously used in other behavioral pharmacology studies. At the time of the current study, none of these animals had participated in another pharmacological study for at least 2 months. Animals were housed in individual primate cages under controlled conditions of humidity ($50 \pm 5\%$), temperature ($24 \pm 1\ ^\circ C$), and light (12 hours light/12 hours dark cycle). Veterinarians skilled in the care and maintenance of nonhuman primates supervised animal care. All procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Chinese Academy of Medical Science Institute of Laboratory Animal Science ethics committee.

2.2. Behavioral testing

Animals were food restricted and received water ad libitum. For testing, animals were transferred from the home cage to a testing cage located in a dimly lit, sound attenuated, ventilated cubicle away from the colony. Each testing cage was equipped with a Cambridge Neuropsychological Test Automated Battery (CANTAB; Lafayette Instruments, Lafayette, IN, USA) apparatus. CANTAB stations consisted of a touch sensitive monitor, a reward delivery system, and a pellet receptacle located to the lower right side of each panel. All animals were previously trained to perform the CANTAB versions of paired associate learning (PAL) and delayed matching to sample (DMTS) tasks.

The DMTS task is a nonspatial working memory task. The task begins with a sample stimulus presented to the animal in the center of the screen for 5 seconds. The sample then disappears from the screen for a delay interval ranging from 0.1 to 75 seconds, and then 2 choice stimuli appear randomly in either the top left, bottom left, top right, or bottom right of the touch-sensitive screen. One of the 2 samples is identical to the stimulus presented during the sample phase and 1 stimulus is new. A response to the same stimulus presented during the sample phase is recorded as a correct choice and results in a positive sound and delivery of reinforcement (sugar pellet). A response to the new stimulus is recorded as incorrect and results in a different sound, a time out (10 seconds), and no reinforcement. A test session consisted of 40 trials divided equally into blocks of 8 trials each at 5 delays. The actual delay parameters were designed to result in performance of at least 85%–90% correct responses at the shortest delay and progressively deteriorating performance leading to performance of approximately 50%–60% correct responses at the longest delays. The total number of errors at each delay was analyzed.

The PAL task involves learning to associate visual stimuli with distinct spatial locations on a trial-by-trial basis. This is a complex task with attention, memory, and executive function components. At the easiest level of this task, a single stimulus is presented in different possible locations on the touch-sensitive screen and in the response phase, the animal must touch the stimulus in the same location in which was originally shown. On more difficult trials (containing 2 or 3 different stimuli), each stimulus is presented consecutively with a 1-second delay between presentations. After all stimuli have been presented, 1 of the sample stimuli is presented again in 2 or 3 different locations on the screen. The animal must touch the target location in which the stimulus was originally presented in order to receive a reward. If an animal fails to successfully complete a trial, the same trial is presented again, up to 6 times. If an animal still fails at the sixth presentation, the trial is aborted and the system moves to the next trial (also referred to as a sequence). Each testing session consisted of 10 trials (or sequences), each at the following levels of task difficulty (in ascending order of difficulty): 1 stimulus, 2 locations; 1 stimulus, 3 locations; 2 stimuli, 2 locations; and, 3 stimuli, 3 locations.