UNIVERSITY OF PÉCS

Doctoral School of Biology and Sportbiology

Investigation of cholinergic modulation of attention and working memory by behavioral pharmacological methods in rhesus monkeys

PhD thesis

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INTRODUCTION

Attentional and memory functions play an important role in the optimal processing of stimuli from the environment. Attentional functions are important both in the processing of current events and in the prediction of expected future events. Attention ensures sensory and motor preparation for upcoming events within a certain time scale. Temporal expectation is the part of attention that prepares the nervous system for the time and probability of an event occurring, but not necessarily consciously or intentionally (Nobre and van Ede 2018). Optimal working memory (WM) is needed to provide appropriate responding to environmental stimuli. Information in working memory is readily available and can be used immediately to plan and implement behavior (Cowan 2008; Miller et al. 1960).

The cholinergic system and acetylcholine (ACh) play essential roles in attention (Lawrence and Sahakian 1995) and memory functions (Drachman 1974). Deficiencies affecting the cholinergic system in neurocognitive disorders (e.g. Alzheimer's disease) adversely affect attention and memory functions (Blokland 1995; Everitt and Robbins 1997; White and Ruske 2002). Acetylcholinesterase enzyme inhibitor donepezil is used to relieve the symptoms of Alzheimer's disease (Hampel et al. 2018).

Behavioral pharmacological methods can be used to better understand the efficacy of candidate drug compounds. In non-human primates, attentional functions can be assessed using the Psychomotor Vigilance Task (PVT) and working memory using the Delayed Matching to Sample task (DMTS). Muscarinic acetylcholine receptor antagonist scopolamine is suitable for transient pharmacological modeling of neurocognitive disorders. Based on literature data, scopolamine can induce cognitive impairments similar to the ones observed in Alzheimer's disease, as scopolamine acutely impairs attentional (Klinkenberg and Blokland 2010) and working memory (Taffe et al. 1999) functions. The cognitive-enhancing effect of active substances used against scopolamine induced impairments can be studied in animal. The results of such studies are important in the experimental modeling of neurocognitive symptoms and may contribute to a more accurate understanding of the cellular and behavioral mechanisms of attention and memory processes associated with the cholinergic system.

AIMS

The aim of our study was to investigate the cholinergic modulation of attention and working memory by behavioral pharmacological methods in rhesus monkeys.

Our main objectives:

- **I.** Determination of the effects of temporal expectation and waiting time (foreperiod) on reaction time, in a modified PVT task, in nonhuman primates: Investigation of the role of the cholinergic system in the stimulus-related temporal expectation in non-human primates.
  1. Investigation of the interaction between scopolamine-induced anticholinergic effects and temporal expectation: Can scopolamine treatment slow down the reaction time and change the distribution of the reaction time data by suspending the accelerating effect of the foreperiod?
  2. Investigation of the effect of acetylcholinesterase enzyme inhibitor donepezil on temporal expectation: Does donepezil improve the temporal expectation impaired by scopolamine?
- **II.** Investigation of the role of the cholinergic system in working memory. Determination of the effects of delay on the retention of working memory in Delayed Matching to Sample task, in nonhuman primates.
  1. Investigation of the interaction between anticholinergic effects and working memory in scopolamine-amnesia model: In what delay range does memory performance decrease with scopolamine treatment?
  2. Investigation of the effect of the ACh enzyme inhibitor donepezil on working memory impaired by scopolamine: Does donepezil treatment counteract the delay-dependent performance-reducing effects of scopolamine?

MATERIALS AND METHODS

Subjects

Five young adult male rhesus macaques (*Macaca mulatta*) were included in the PVT study and six in the DMTS study at the beginning of the experiments. All procedures were conducted in the Grastyán Translational Research Center of the University of Pécs. The studies were approved by the Department of Animal Health and Food Control of the County Government Offices of the Ministry of Agriculture (BA02/2000-11/2012). Measures were taken to minimize pain and discomfort of the animals in accordance with the Directive 40/2013 (II.14): "On animal experiments" issued by the Government of Hungary, and the Directive 2010/63/EU "On the protection of animals used for scientific purposes" issued by the European Parliament and the European Council.

Bbehavioral paradigms

A modified PVT task based on reaction time was used to examine attention. Animals performed the modified PVT task in one session per day. Each experimental session consisted of 405 trials and lasted for approximately 60 min. During task performance, animals were seated in a primate chair in front of a computer screen. A response knob with an electric touch sensor was placed at a comfortable reaching distance from the primate chair. At the beginning of each trial, a short tone was played to indicate that the subjects had to touch the response knob and prepare for the key release response. If the animal did not touch the knob within 2 s, the trial was not initiated and an intertrial interval of 2±0.5 s followed. If the sensor knob was touched, a warning stimulus appeared within 0.3 s indicating the start of the foreperiod and remained displayed for the entire duration of the foreperiod. The duration of the foreperiod was set between 1.1 and 9.9 s. When the foreperiod elapsed, the black disc turned white, which served as the target stimulus. The task required the animals to react as quickly as possible to the target stimulus by releasing the knob. If the subject responded while the target was still displayed, the trial was completed correctly. Upon a correct response the target stimulus disappeared, and subjects received a drop of liquid reward immediately after the response.

The effect of pharmacological treatments on working memory was investigated using a DMTS task. Animals individually performed the DMTS task in one session per day in large cubical testing compartments equipped with a touchscreen with LCD monitor. Each experimental session consisted of 120 trials and lasted for approximately 60 min. Each trial

consisted of a sample phase followed by a variable delay and a probe phase. At the beginning of each trial, a short tone was played to indicate the start of the trial. During the sample phase, a stimulus was presented at the center of the screen that the animals had to touch. If the animal did not touch the sample stimulus within 5 seconds, the trial was considered unsuccessful and was terminated with no reward delivered. If the subject responded while the sample stimulus was still displayed, the sample phase was followed by a delay with blank screen. On the experimental sessions we applied 3 delay duration categories: short delay between 1.0 and 1.9 s; medium delay between 15 and 33 s; long delay between 40 and 76 s. After the delay time had passed, the probe phase started, and 4 stimuli appeared in the four quadrants of the screen, one of which was identical to the stimulus presented in the preceding sample phase (target stimulus) and 3 were different (distractor stimuli). During this phase, the animals had 5 s to touch the target stimulus. Upon a correct response the stimuli disappeared, and subjects received a pellet reward.

Procedures and drug administration

In the present studies we applied placebo-controlled crossover and repeated measures experimental design. Treatments were administered as an intramuscular injection prior to the experimental session. Muscarinic ACh receptor antagonist scopolamine was used to induce cholinergic deficits. The ACh esterase enzyme inhibitor donepezil was used to compensate for the decreased performance of attention and memory functions due to scopolamine treatment.

Statistical analysis

To test the interaction between the effect of treatment and foreperiod on RT, we used a linear mixed model on single-trial RT data. To complement the parametric analysis and also capitalize on the rich information contained in the shape RT distributions, RT data was analysed by shift function analysis. Task performance, number of early and late responses, and reaction time were analysed.

In the case of DMTS task we analysed performance accuracy and mean reaction time. We analysed the data using a conventional repeated measures analysis of variance (rANOVA).

RESULTS

Investigation of the effects of cholinergic agents on attention in a modified PVT task

The reaction times were significantly shorter for longer foreperiods in vehicle sessions ($t_{34.7}$= 3.31, p=0.0022). However, foreperiod did not have a significant effect on performance rate ($F_{8,24}$=1.59, p=0.18, η_p^2=0.35).

The analysis of treatment effects showed a marginal main effect on performance rate ($F_{3,9}$=3.28, p=0.073, η_p^2=0.52). In particular, scopolamine treatment significantly decreased performance rate compared to vehicle (p=0.017; *Figure 1A*). Application of 100 μg/kg dose of donepezil significantly reversed the scopolamine-induced impairments on performance rate (p=0.037). Treatments clearly modulated the foreperiod dependence of RT (Treatment×Foreperiod: $F_{3,26.6}$=3.29; p=0.036), therefore, scopolamine treatment abolished the effect of foreperiod on reaction time, which could not be counteracted by donepezil treatment (*Figure 1B*).

Scopolamine treatment increased reaction time relative to vehicle across the whole reaction time distribution, but particularly in the case of slower reaction time, creating a strong tail of slow responses. This slow response component probably reflects attentional lapses. Mirroring the effect of scopolamine, donepezil was more effective in the slower reaction time deciles, that is, it reduced the number of lapses. In the control treatment longer foreperiods induced shorter reaction times, especially in faster deciles. Scopolamine treatment abolished the foreperiod dependence across the whole reaction time distribution.

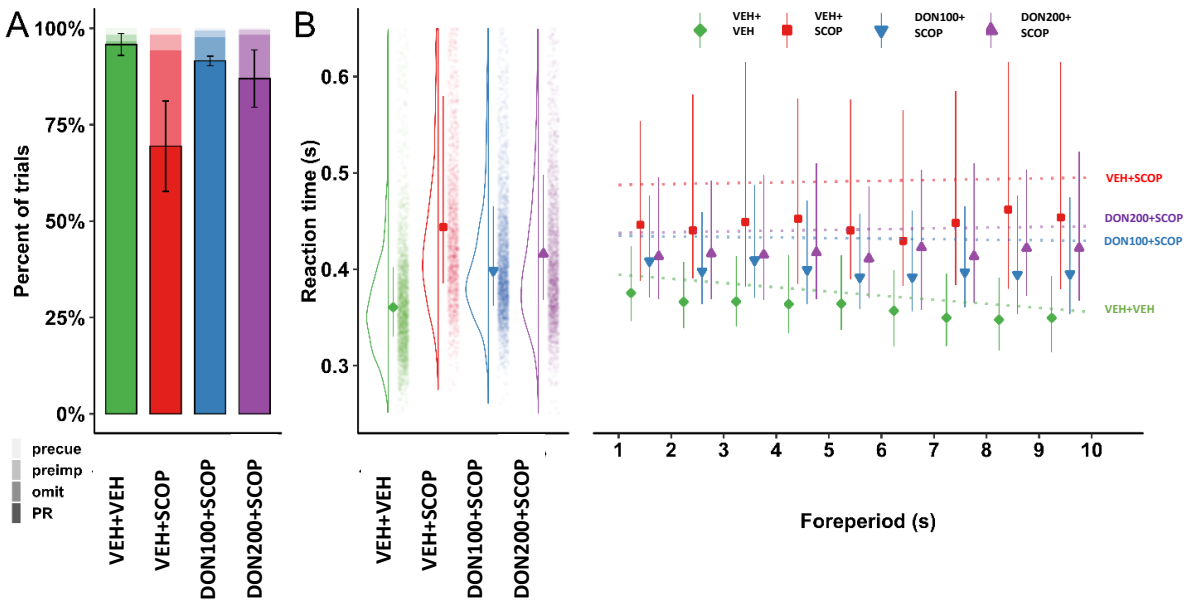

Figure 1: (A) Scopolamine impaired and co-administered donepezil partially restored average performance. Bars with black contours filled with opaque colours show group mean performance rate (PR), error bars show standard error of mean (s.e.m). **(B)** Scopolamine impaired and co-administered donepezil partially restored average reaction time, however the temporal expectation eliminated by scopolamine was not restored by donepezil. On the left, RT distributions for each treatment are shown. The marker in the middle indicates the group mean of individual medians, the error bars cover the range from the 2nd to the 9th deciles (also group averages). The distributions of RTs pooled across subjects and sessions are also visualised with kernel smoothing (to the left) and as jittered dotplots (to the right, each dot is one trial). The right part of the plot shows RT for each 1-sec bin of foreperiod length, with markers and error bars using the conventions described above (group averaged 2nd, 5th and 9th deciles). Dotted lines correspond to the linear relationship between foreperiod as a continuous variable and RT as modelled by the linear mixed model. Note that the distance between the marginal means of the linear model and the medians is commensurate with the skewness of the RT distribution.

Investigation of the effects of cholinergic agents on working memory in the DMTS task

In the vehicle treatment, memory performance accuracy decreased continuously across the whole delay period ($F_{2,10}$=16.842; p<0.001; η_p^2=0.77).

Scopolamine pre-treatment substantially deteriorated task performance on average ($F_{1,5}$=18.133; p=0.008; η_p^2=0.78) while also significantly changing the delay-accuracy function so that it reached its lowest point already in the medium delay period and did not decrease further ($F_{2,10}$=5.213; p=0.028; η_p^2=0.51). Post hoc comparisons of the time-binned average accuracies in the scopolamine condition from the rANOVA also confirmed this (SHORT vs. MEDIUM p<0.001; MEDIUM vs. LONG p=0.438). Donepezil co-administered with scopolamine partially reversed the impairments in accuracy caused by scopolamine (TREATMENT x DELAY: $F_{4,20}$=2.985; p=0.044; η_p^2=0.37; *Figure 2A*). Specifically for medium-length delays, performance accuracy was better than the corresponding scopolamine performance (100 μg/kg: p=0.025; 200 μg/kg: p=0.005; *Figure 2B*).

The average reaction time was not significantly impaired by scopolamine treatment ($F_{1,5}$=3.681; p=0.113; η_p^2=0.42). The delay length had a significant effect on the average reaction time ($F_{2,10}$=66.217; p<0.001; η_p^2=0.93). Donepezil treatment did not have significant effect on reaction time compared to scopolamine ($F_{2,10}$=1.643; p=0.242; η_p^2=0.25). In the case of donepezil treatment, a significant main effect was observed in the delay length ($F_{2,10}$=25.392; p<0.001; η_p^2=0.84). In the reaction time no interaction was observed between treatments and delay (VEH vs. SCOP: $F_{2,10}$=0.22; p=0.804; η_p^2=0.04; SCOP vs. DON: $F_{4,20}$=1.079; p=0.393; η_p^2=0.18).

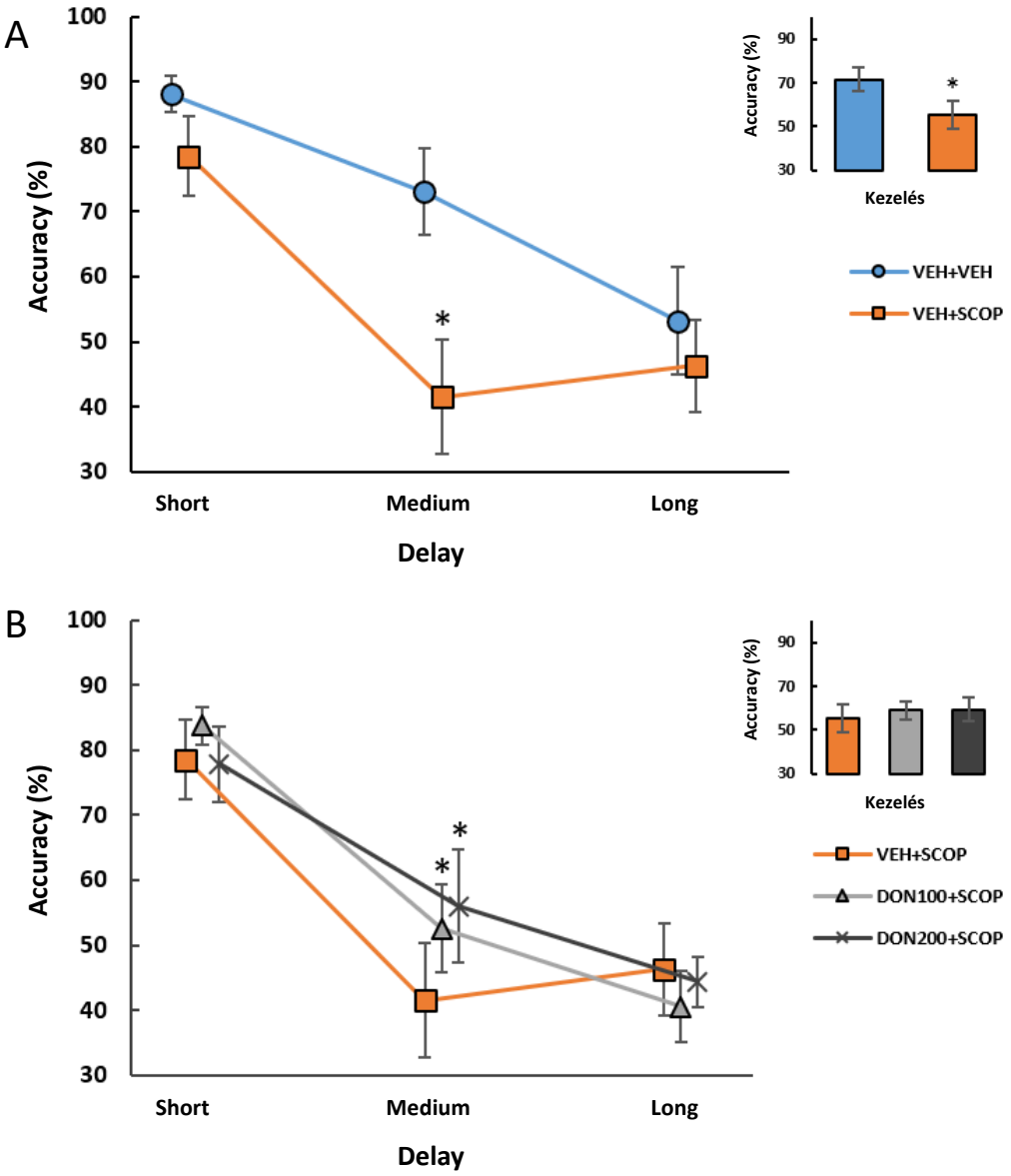

Figure 2: (A) Scopolamine impaired, while **(B)** co-administered donepezil partially restored performance rate (accuracy) in the medium delay (Medium) condition. Error bars show standard error of mean (s.e.m). Asterisks mark significant ($p<0.05$, post hoc) differences compared to the vehicle control condition within each level of Delay (Short, Medium, Long).

DISCUSSION

The effect of foreperiod has been described previously in primates (Sharma et al. 2015), but the effect of modulation of cholinergic neurotransmission on foreperiod-induced changes on reaction time is not yet clear. In our study, scopolamine treatment completely abolished the effect of FP on reaction time. A possible reason for the impairing effect of scopolamine on temporal expectation is that scopolamine may inhibit the FP-induced cholinergic activation in prefrontal cortex, which is essential in optimal stimulus detection (Parikh et al. 2007). This may be due to the scopolamine induced elimination of the effect of temporal expectation in the fast reaction time components. Donepezil was able to compensate the mean reaction time slowdown caused by scopolamine. However, in the case of long foreperiod the fast reaction time components did not improve with donepezil treatment, thus the temporal expectation showed no improvement. Based on these we assume that donepezil improves general alertness when used against scopolamine, however, it has no effect on the temporal expectation.

Based on our results in the DMTS test, in the case of vehicle treatment, cognitive performance decreases monotonically with increasing delay time and reaches a minimum level during the long delay. This is suggestive of a rightward instead of a downward shift of the performance accuracy curve, implying that it is primarily the pace, not the depth of delay-dependent short-term memory deterioration that changed as a result of scopolamine treatment. This is supported by the fact that scopolamine had no impairment effect on cognitive performance in the short delay, also in accordance with previous results (Bartus and Johnson 1976; Terry et al. 1993). We have shown that donepezil is able to partially reverse the delay-dependent impairments caused by scopolamine, such as a decrease in cognitive performance in the medium delay (15-33 s) condition. Thus, donepezil treatment restores a pattern of cognitive performance similar to the control condition. Our results suggest that the modulation of WM temporal maintenance by scopolamine and donepezil treatments in our studies may have been due to transient degradation and partial restoration of mACh receptor-associated, persistent, stimulus-coding mechanisms in memory networks.

SUMMARY

I. The main results in the modified PVT task:

1. As a validation of the modified PVT paradigm, we confirmed, that by increasing the time elapsed between appearance of warning and target stimuli the reaction time decreased in rhesus macaques. Based on the decreasing reaction time, the PVT paradigm is suitable for detecting the effect of temporal expectation on reaction time.
2. Scopolamine treatment caused a slowing of the mean reaction time, and the distribution of reaction time data also shifted towards slow responses, indicating an increase in the number of lapses which suggests a decrease in alertness. Furthermore, scopolamine treatment abolished the accelerating effect of foreperiod on reaction time, indicating a loss of temporal expectation.
3. Donepezil treatment reduces the mean reaction time and the number of lapses, indicating an improvement in alertness. However, donepezil treatment did not restore the accelerating effect of waiting time on reaction time, so donepezil treatment alone is not sufficient to compensate the impairments by scopolamine caused in temporal expectation.

II. The main results in the DMTS task:

1. As a validation of the DMTS paradigm, we confirmed, that with the increase of delay duration (1-76s) the ability to retain elements stored in the WM is constantly declining, resulting in lower performance. With this, we confirmed, that our paradigm is suitable for detecting natural WM degradation occurring with time.
2. We found that the effects of anticholinergic scopolamine depend on the length of the delay period and has a particularly detrimental effect on task performance in the medium (15–33 s) delay period. This result suggests that scopolamine treatment accelerates the normal deterioration of WM.
3. Furthermore, our results show, that donepezil partially reverses the impairments caused by scopolamine in the medium delay period, which suggests that donepezil may be suitable for slowing the degradation of WM.

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