

Interplay Between Muscarinic and Dopamine Receptors Activity on Retrieving Hippocampal Dependent Memories in Male and Female Mice

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ABSTRACT

Episodic memory retrieval is essential phenomenon ensuring successful animals and human survival. Muscarinic receptors play significant role in memory and have displayed gender dimorphic influence in retrieving hippocampus dependent memories. D2 type dopamine receptors impact memory by modulating cholinergic neurotransmission in brain, however, majority of existing data is derived from male subjects only. This study was conducted to assess the effects of D2 and muscarinic interplay on retrieval and the influence of gender. Balb/C mice of both genders were trained for hippocampus dependent fear and spatial memories using contextual fear conditioning and Morris water maze, respectively. Sub-chronic treatment for dopamine and muscarinic receptor modulation was done by intraperitoneal administration of D2 antagonist risperidone alone and with muscarinic blocker scopolamine or acetylcholine esterase inhibitor donepezil (dose: 2.5mg/kg, 1mg/kg and 1 mg/kg respectively), memory retrieval was assessed. Donepezil and risperidone co-treatment reduced retrieval of spatial memory in male only ($p < 0.05$). In males fear retrieval was impaired by simultaneous antagonism of both receptor types ($p < 0.05$) in contrary to females where fear recall was significantly enhanced ($p < 0.05$). Our findings suggest that interplay between Dopamine and muscarinic receptor activity on memory retrieval depends on task and gender.

Keywords: Dopamine D2 Receptor, Episodic Memory, Gender, Muscarinic Receptor, Scopolamine.

INTRODUCTION

Episodic memories are hippocampus dependent memories which are essential for everyday functioning of humans and animals. Muscarinic receptors are type of cholinergic receptors that are crucial in formation and retrieval of hippocampus dependent memories (Leaderbrand et al.; Hasselmo). Hippocampus dependent memory are also associated with dopamine neurotransmission. Studies have shown that dopamine signaling via D2 receptor type modulate cholinergic signaling by effecting muscarinic activity (Martorana et al.; Ichikawa et al.). In our previous experiments we found gender dimorphic effect of muscarinic receptors in hippocampus depend memory retrieval. Considering the influence of dopamine D2 receptors on muscarinic receptor function, current study was conducted to unveil the role of interplay of both receptor types on hippocampus dependent memories and the effect of gender.

METHODOLOGY

Balb/C mice (age 3-4 months) were trained for contextual fear and water maze test following which they were randomly divided into four male and four female groups i.e., control (group 1) and three treatment groups treated with 2.5 mg/kg risperidone alone (group 2), or with 1 mg/kg scopolamine (group 3) and 1mg/kg

donepezil (group 4). Memory retrieval was tested following 5 days of treatment. One way ANOVA and Bonferroni's post hoc test were used for data analysis.

RESULTS

Role of risperidone and muscarinic modulators on retrieving spatial memory:

Figure 1 is showing the effect of risperidone and muscarinic modulators on spatial memory retrieval in mice. Spatial memory was evaluated by measuring the time spent by animal in the platform quadrant during test trial and the number of hidden platform location crossing. We found that D2 antagonism alone did not cause any significant difference in retrieving spatial memory in both genders. However, risperidone co-administered with donepezil impaired retrieval of spatial memory in male animals only. This effect was contrary to our previous experiments showing retrieval improving influence of donepezil in scopolamine induced retrograde amnesia in mice.

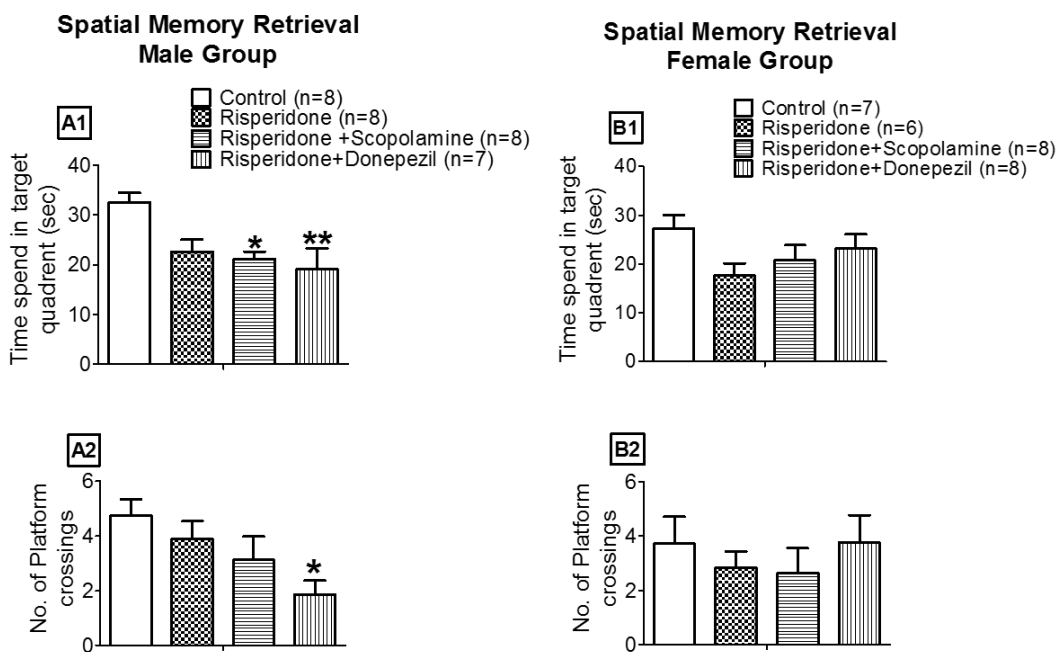


Figure 1. Effect of dopamine and muscarinic receptor modulation on spatial memory retrieval. Data is presented as mean \pm SEM. $P^* < 0.05$ and $p^{**} < 0.001$ compared to control. n is sample size per group.

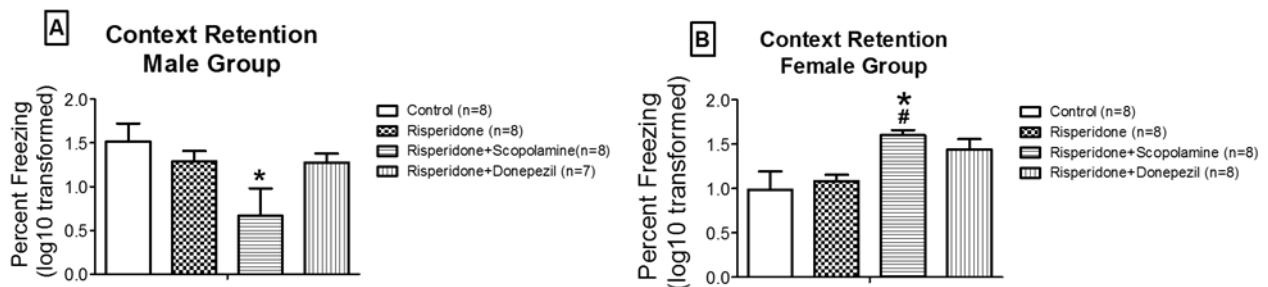


Figure 2. Effect of dopamine and muscarinic receptors on fear memory retrieval. Data is presented as mean \pm SEM. $*P < 0.05$ compared to control and $\#p < 0.05$ compared to risperidone group.

Effect of risperidone and scopolamine on fear memory retrieval:

Contextual fear retrieval is hippocampus dependent function. Fear in rodents is measured as freezing which is the immobile state of rodent in response to any aversive or frightening situation. Simultaneous muscarinic and D2 antagonism imparted a gender dimorphic effect on retrieving contextual fear by impairing freezing in males while significantly enhancing the fear response in female animals compared to their respective untreated controls.

CONCLUSION

Thus, it is concluded that interplay between muscarinic and dopamine D2 receptors influence hippocampus dependent spatial and contextual fear memory retrieval in gender dependent fashion.

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REFERENCES

1. Hasselmo, M. E. "The Role of Acetylcholine in Learning and Memory." *Curr Opin Neurobiol* 16 6 (2006): 710-5. Print.
2. Ichikawa, J., et al. "Atypical, but Not Typical, Antipsychotic Drugs Increase Cortical Acetylcholine Release without an Effect in the Nucleus Accumbens or Striatum." *Neuropsychopharmacology* 26 3 (2002): 325-39. Print.
3. Leaderbrand, K., et al. "Muscarinic Acetylcholine Receptors Act in Synergy to Facilitate Learning and Memory." *Learn Mem* 23 11 (2016): 631-38. Print.
4. Martorana, A., et al. "Dopamine D(2)-Agonist Rotigotine Effects on Cortical Excitability and Central Cholinergic Transmission in Alzheimer's Disease Patients." *Neuropharmacology* 64 (2013): 108-13. Print.
5. Rashid, H., and T. Ahmed. "Gender Dimorphic Effect of Dopamine D2 and Muscarinic Cholinergic Receptors on Memory Retrieval." *Psychopharmacology (Berl)* 238 8 (2021): 2225-34. Print.