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The Effects of Sex and Muscarinic Activity on Memory Retrieval in a Brain Injury Mouse Model

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Introduction

Following brain injury, either scopolamine or donepezil was given to each group for 5 days. Acute scopolamine administered immediately following brain trauma had a neuroprotective effect only in males, whereas subchronic donepezil significantly impaired neurological functioning in both sexes. In male mice, subchronic scopolamine and donepezil treatment reversed TBI-induced retrograde amnesia for spatial memory. TBI and treatments had no effect on contextual fear memory retrieval in either sexes. As a result, we concluded that the muscarinic receptors' sex-dimorphic response in TBI-induced memory impairment is dependent on the type of memory. This study emphasises the possibility of therapeutic modalities in TBI patients.

Traumatic brain injury is a brain injury caused by an unexpected force that causes changes in normal brain functioning. It is a major cause of death and neurological disability. TBI causes significant cognitive deficits in memory, information processing, and behaviour. TBI can be caused by a variety of factors, the most common of which are traffic accidents, falls, and blast injuries. Men are three times more likely than women to suffer from TBI. Injuries, particularly TBI, have a biological mechanism that includes inflammation, edoema, dysregulation of neurotransmitter systems, oxidative stress, and mitochondrial dysfunction. TBI has been linked to an increased risk of developing neurodegenerative diseases, and it has been linked to the early onset of Alzheimer's disease. Sex is a significant factor in post-TBI cognitive outcomes.

Experiments in female rodents under physiological conditions revealed neuroprotective potential and better recovery from mild TBI-induced cognitive effects, but not in males. The precise mechanism of this neuroprotection in females versus males is not fully understood. Endogenous female hormones are thought to provide neurological protection following a TBI in young female rats but not in males. TBI interferes with learning and memory processes by impairing memory acquisition, consolidation, and retrieval. TBI causes memory loss by interfering with cholinergic transmission, which is essential in learning and memory processes. In animals after mild TBI, there is a decrease in acetylcholine synthesis and release in the hippocampus. Mild TBI has been linked to a decrease in hippocampal muscarinic cholinergic receptors after the insult [1].

Description

Traumatic brain injury is a major global risk factor for cognitive impairment and neurodegenerative diseases. Cognitive and memory impairment after a TBI is associated with dysregulation of cholinergic neurotransmission in subjects' brains. The severity of memory impairment following a TBI is related to the subject's gender. The purpose of this study was to determine the sex-dimorphic role of muscarinic cholinergic modulation in neurological functioning and episodic memory retrieval in a TBI mouse model. Balb/c mice were divided into four male and four female groups. Except for the Sham mice, all groups were subjected to brain injury J impact force) after training with the Morris water maze test and fear conditioning.

With the importance of sex dimorphism in post-TBI cognitive outcomes and the potential role of muscarinic receptor modulation in treating TBI-induced memory impairment in mind, the purpose of this study was to determine the influence of sex on the role of the muscarinic receptor in reversing TBI-induced neurological and memory recall deficits in young mice. Memory retrieval function was evaluated using the Morris water maze and context retention testing. To determine neurological, locomotor, and exploratory functioning, neurological severity scoring was used. Subchronic muscarinic modulation had a task-dependent sex-dimorphic effect in reversing mild TBI-induced memory retrieval impairment [2].

Following a concussion, the neurological outcomes are determined by sex and cholinergic neurotransmission. We investigated the role of muscarinic receptors in episodic memory retrieval following mild TBI in age-matched male and female mice. Our findings showed that acute muscarinic activation after trauma exacerbated TBI-induced neurological dysfunction in males but not in females. Donepezil-induced subchronic neurological dysfunction in male and female TBI mice. TBI impaired spatial memory retrieval in all mice, regardless of gender. TBI-induced spatial recall impairment in males could be reversed with subchronic scopolamine and donepezil. Doran et al. report a recent breakthrough in determining the underlying cause of sex-dimorphic responses to post-TBI neuronal outcomes. They discovered a significant infiltration of proinflammatory cells in male mice brains compared to females. This distinct neuroinflammatory process has been proposed as a possible explanation for gender differences in post-TBI neuronal outcomes and recovery.

Previous research has shown that scopolamine has time-dependent effects on TBI brains, with neuroprotection immediately after injury and neurodegeneration when administered later. In our experiment, this effect was observed in a sex-biased manner, i.e., this response was only observed in males. Female TBI mice recovered better from the trauma in terms of neurological functioning than male TBI mice, corroborating previous findings that females are more resistant to TBI-induced neuronal damage than males. Though the underlying mechanisms of this sex-dimorphic neuroprotection to post-TBI outcomes in females are not fully understood, female gonadal hormones have been linked to improved neurological recovery after brain injury [3-5].

Conclusion

To our knowledge, this is the first study to compare the effects of muscarinic receptor modulation on episodic memory retrieval in male and female mice with mild TBI. The current study has a limitation in that the effect of muscarinic drugs on memory retrieval was assessed at a relatively early time point, after brain injury. The majority of the cognitive outcomes of mild TBI occur later in the subjects' lives. Furthermore, future research should focus on histological and synaptic changes in order to gain better mechanistic insights for therapeutic purposes. According to our findings, muscarinic receptor activity is required

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to reverse TBI-induced spatial memory retrieval impairment in males only, whereas fear memory retrieval is unaffected by muscarinic modulation in TBI-affected mice of both sexes. Thus, the muscarinic receptors' sex dimorphic effect in reversing TBI-induced retrograde amnesia is dependent on the type of memory.

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Conflict of Interest

There are no conflicts of interest by author.

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