



Preserved Memory Function of Rats Following Fluorouracil Treatment

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2019/v30i330269

Editor(s):

- (1) Dr. Vasudevan Mani, Associate Professor, Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraidah, Kingdom of Saudi Arabia.
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Reviewers:

- (1) Michael Bordonaro, Geisinger Commonwealth School of Medicine, USA.
(2) D. Ramachandrareddy, Vinayaka Missions University, India.
Complete Peer review History: <http://www.sdiarticle4.com/review-history/51964>

Original Research Article

Received 01 August 2019
Accepted 04 October 2019
Published 14 October 2019

ABSTRACT

Chemotherapy is widely used to treat cancers, but can have undesirable secondary effects, such as cognitive impairment. Fluorouracil (5-FU) is a chemotherapeutic agent that is combined with other agents to treat different types of cancer, such as breast, prostate and brain cancer. 5-FU has been reported to pass the blood-brain barrier, but its effects on cognition are not yet well established. The aim of this study was to evaluate the effects of 5-FU on memory function. 5-FU was injected intraperitoneally into rats. 5-FU did not impair memory function determined using the Y-maze and novel object recognition behavioral tests. Therefore, it is concluded that fluorouracil itself does not induce the memory impairment of chemobrain.

Keywords: Chemotherapy; fluorouracil; memory impairment; chemobrain.

1. INTRODUCTION

The experience of cognitive deficits following chemotherapy is a phenomenon known as

“chemobrain” [1] and is a serious complication for cancer survivors [2,3]. Chemotherapy can induce many side effects, such as fatigue, pain, hepatotoxicity, and memory loss [4,5]. Long-term

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cognitive impairment affects the quality of life of cancer survivors. Studies, both experimental and clinical, have reported some short-term cognitive deficits after chemotherapy treatment. Cognitive deficit caused by chemotherapy extends from 17% to 75% of cancer survivors [6]. In this study, the effects of the chemotherapeutic agent fluorouracil (5-FU) on memory function were tested.

5-FU is an anticancer drug commonly used in the treatment of many types of cancer, such as brain, colorectal, and breast cancers [7,8]. 5-FU has the ability to pass the blood–brain barrier (BBB) and it is hypothesized that chemotherapeutic agents that cross the BBB may induce memory dysfunction [9,10]. The exact mechanism of chemobrain is still elusive. Therefore, the goal of the present study was to investigate the effect of 5-FU on memory function.

2. MATERIALS AND METHODS

2.1 Animals

Sixteen male rats (10–11-weeks-old and about 18–30 g) were housed individually and maintained in a 12-h:12-h light:dark cycle (lights on 6:00 am) in Qassim University's animal house, in a controlled and pathogen-free environment (25°C), with free access to water and a standard chow diet. The animals were observed daily for any changes and to check mortality. Behavioral tests were done during the light period. The rats were divided into two groups and each group had 8 animals.

2.2 Drug Administration

The rats received three doses (one every other day) of saline and 5-FU (50 mg/kg, intraperitoneally). After that, the animals were subjected to behavioral tests one day after the last dose.

2.3 Assessment of Spatial Memory Using Y-maze

The Y-maze test assesses the ability of animals to distinguish places they have already explored and their propensity to explore new places [11]. The Y-maze was made for the rats using wood and had dimensions 50 × 10 × 15 cm. The arms were each at 120° to the other arms and were painted brown for easy visualization of rats during testing. The Y-maze apparatus was placed on the floor, and a light was placed on top

of each arm to ensure equal light distribution. A camera was used to record all the testing sessions. The Y-maze tests evaluated the spatial memory of the rats by providing different cues (circles, triangles, and later X) at the end of each arm.

In this experiment, there are two sessions: the training session and the testing session. In the training session, rats were permitted to freely explore two arms (the start arm, in which they were placed, and the familiar arm, located either to the left or right of the start arm). This session takes 15 min. During the second, testing session, after 3 h, rats were placed in the same arm as in their training session for 5 min. The rats were allowed to explore the entire maze, including the new arm. The testing session was video recorded. The number of entries into—and the time spent in—the new arm were scored and analyzed [12]. The rats were considered to have entered an arm when more than half of their body entered it.

2.4 The Novel Object Recognition Test

The NOR test is a behavioral test that evaluates memory function [13]. The test apparatus was made of wood, and the dimensions of the box were 40 × 40 × 40 cm. The objects used in this test were two teacups, and the novel object was a rectangular box similar in size to the teacups. In this test, the rats were introduced to and allowed to explore the teacups for 10 min, then they were returned to their cages for 3 h. The rats were then brought back for a 5-min testing session with one of the teacups replaced with the novel object. The time spent exploring the novel object was recorded using a camera, measured, and the results were analyzed [14].

2.5 Data Analysis

The results are presented as group means ± S.D. and were analyzed using Graphpad Prism 5 software. Data were analyzed using an unpaired Student's *t*-test. $p \leq 0.05$ was considered statistically significant.

3. RESULTS

3.1 Behavioral Performance in Y-maze

In this study, rats were treated with 5-FU and compared with an saline treated group. There was no significant difference between the two groups in total time spent—or number of entries into—the novel arm of the Y-maze (Fig. 1).

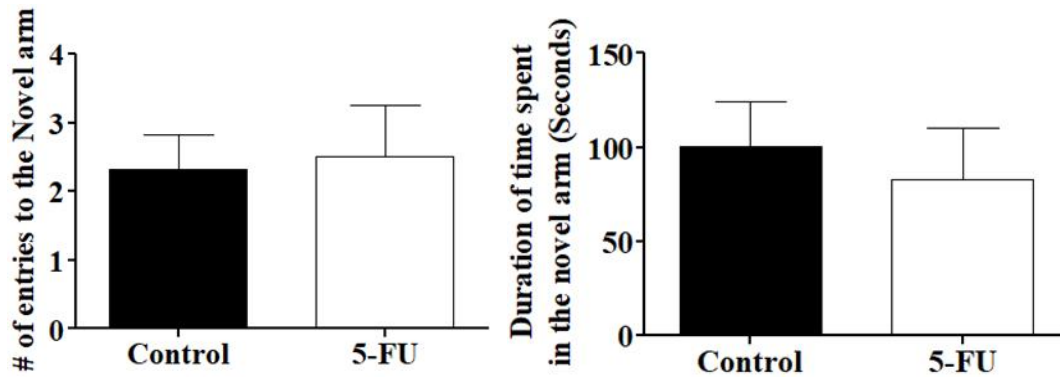


Fig. 1. Y-maze test performance (n = 8 rats/group). The 5-FU-treated rats showed no significant difference in memory function compared with saline treated (control) rats. There was no statistically significant difference between the 5-FU-treated and control rats in either the number of entries or the dwell time spent in the novel arm of the Y-maze

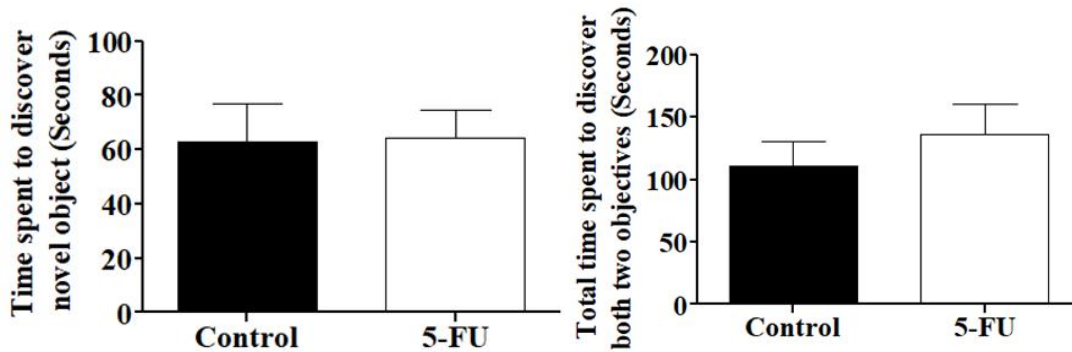


Fig. 2. Novel Object Recognition (NOR) test results. There was not a statistical significant difference in the treated and control groups' NOR test results were found

3.2 Effects of 5-FU Treatment on the NOR Test

No significant difference was found between the saline and 5-FU groups in the NOR test in either the training or testing sessions.

4. DISCUSSION

The current study examined the effect of 5-FU on memory function in rats using two behavioral tests—the Y-maze and NOR. In chemotherapy protocols, several chemotherapeutic agents are often combined to avoid drug resistance and to be more effective. Previous clinical and experimental studies have identified impaired memory function as an effect of chemotherapy [15,16]. This study aimed to evaluate the effect of 5-FU on memory function when administered alone.

Chemotherapy uses cytotoxic agents, including 5-FU. Thus, treatments using this drug, over time, could result in impaired working and spatial memory. A previous study using rats showed that combined cyclophosphamide, methotrexate and 5-FU (known as the CMF regimen) impairs memory as determined by the NOR test [17]. Several lines of evidence have shown that chemotherapy and cognitive dysfunction are correlated [18]. Although the exact etiology of the phenomenon is not clear, it is reported that it could be a result of neuroinflammation, an alteration in protein expression, and/or reduced neurogenesis [19,20]. In this study, two behavioral tests were performed to examine memory function in rats treated with 5-FU. No memory impairment was detected using the Y-maze and NOR tasks following the 5-FU treatment. These data suggest that 5-FU itself (i.e. administered alone) does not affect memory function in rats.

Although, these results are inconsistent with the general findings with the chemotherapeutic drugs, but studies conducted in the past have also indicated that anti-cancer drugs do not always affect the memory functions in experimental conditions [21]. The variations in the drugs' response was found to be due to species, strains of the animals that were used for the study, since permeability through the blood-brain barriers is an important parameter to induce cognitive impairment. Dosing and duration of therapy is also reported to play a significant role in affecting the brain functioning of the animals [22,23].

5. CONCLUSION

Chemotherapy is known to have a direct effect on improving the survival rate of cancer patients. However, the limitation of the use of chemotherapy is its toxicity. Clinical studies and reports have demonstrated that cancer patients who have received chemotherapy have developed cognitive impairments, which have also been reported in chemobrain model rodents. The present study tested the effect of 5-FU on memory function using a Y-maze behavioral test. The study's results conclude that 5-FU has no effect on memory function when tested in three doses. Further studies with long-term exposure with 5-FU is suggested to evaluate the precise of the drug on memory.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This research was approved by the research unit at the College of Pharmacy at Qassim University under ID number 2019 - CP - 5.

ACKNOWLEDGEMENTS

I would like to thank college of Pharmacy, Qassim University for the support and facility.

COMPETING INTERESTS

Author has declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not

intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Peer-review history:
The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/51964>