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Impaired learning and memory: a fallout of metronidazole induced neurotoxicity

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Abstract

Background: Metronidazole, an old warhorse in treatment of anaerobic, parasitic as well as bacterial infections in human and veterinary medicine has been observed to have neurotoxic adverse effects. An increase in the existing knowledge on the mechanisms of metronidazole-induced neurotoxicity is necessary.

Objective: To evaluate the effects of metronidazole on memory and learning in adult rats.

Methods: Eighty adult rats were allotted to 4 groups (n=20). Group 1 was given 5 mL/kg 0.5% Tween-80®, group 2 was treated with 50 mg/kg metronidazole, group 3 was given 1 mg/kg risperidone, group 4 was treated with metronidazole 50 mg/kg + risperidone 1 mg/kg. All drug administrations were done daily for 28 days using the oral route. On the 28th day the rats were exposed to tests that evaluated cognitive function like the hole-board, Morris water maze and Y-maze test.

Statistical analysis used: One-way ANOVA followed by Dunnet's post hoc test for multiple comparison. Statistical differences were considered significant at $p<0.05$.

Results: Metronidazole impaired memory acquisition and learning, and reduced reference memory index (RMI) on the hole board, increased the escape latency in the Moris water maze, and reduced percentage alternation and spatial recognition memory in the Y-maze ($p<0.01$). Co-administration of metronidazole with risperidone reversed all the memory and learning deficits in the treated rats

Conclusion: In conclusion, it is suggested that metronidazole induces cognitive dysfunction by stimulating 5-HT_{2A} receptors in the CNS.

Keywords: Neurotoxicity, Memory and learning, neurotransmission, metronidazole, cognitive dysfunction

INTRODUCTION

The nervous system is a complex biological system containing delicate structures such as neurons, dendrites, and glial cells. The nervous system is also equipped with a selectively permeable membrane, which provides a selective defense system [1]. The complex nature of the nervous system also makes it highly vulnerable to even the minutest disruption of its environment, and structure of function [2]. Disruption of the innate equilibrium of the nervous system may result in consequences ranging from mild reversible to severe irreversible damage [3]. Evidence of a disrupted nervous system or toxicity may manifest immediately upon exposure or may be delayed and may include encephalopathy, cognitive and behavioral dysfunction, and movement disorders or numbness [4]. A collection of these symptoms is known as neurotoxicity and it occurs due to the alteration of neuronal structure and/ or function by iatrogenic processes or exposure to neurotoxicants,which may act on the neuronal cells or disrupt their metabolism [4].

Metronidazole is a commonly used antibacterial and antiprotozoal agent, with a good level of tolerance [5], but it has been observed to have neurotoxic adverse effects associated with its use [6]. There have been reported occurrences of encephalopathy, damage to the cerebellum, and other neurologic adverse effects [7]. Susceptibility to metronidazole-induced neurotoxicity is not sex-selective and more adult cases have been reported even though there have been a few pediatric cases as well [7]. Peripheral neuropathies have been reported in human cases of metronidazole-induced toxicities, other reported symptoms include, tremors, ataxia, dizziness, and seizures [8]. Cerebellar dysfunctions resulting in ataxia, nystagmus, head tilt, tremors, and seizures have been reported in dogs and cats [9]. A systematic review showed that cerebellar dysfunction (75%), altered mental status (33%) and seizures (12%) were most common among patients with metronidazole neurotoxicity [6].

The mechanism of metronidazole-induced neurotoxicity remains sketchy, although various researchers [10] have put several theories forward. This study is geared towards increasing the existing knowledge on the currently vague pathophysiologic mechanisms of metronidazole-induced neurotoxicity. Here we report the effects of metronidazole on learning and memory.

MATERIALS AND METHODS

Metronidazole and risperidone (Sigma, St. Louis, MO, USA) were bought from Merck chemicals and reagents, Lagos, Nigeria, and normal saline (Fidson health care, Nigeria, bought from Mimshach Pharmacy LTD, Bayelsa state.

Experimental Animals

For this study, 80 albino rats with an average weight of 120.5 g were housed in 20 different cages, with separate cages for males and females (maximum of 5 rats per cage) to avoid overcrowding. The

animals were maintained on normal rodent feed (Topfeeds, Calabar, Nigeria) and had free access to drinking water. Ethical approval was obtained from the institutional animal and ethics committee. All animals were handled by standard protocols,11 and ARRIVE 2.0 guidelines for handling animals (https://arriveguidelines.org/arrive-guidelines/sample-size).

Methods

Effect of metronidazole on memory and learning

Eighty adult rats were allotted to 4 groups (n=20). Group 1 was given 5 mL/kg 0.5% Tween-80®, group 2 was treated with 50 mg/kg metronidazole, group 3 was given 1 mg/kg risperidone, group 4 was treated with metronidazole 50 mg/kg + risperidone 1 mg/kg. All drug administrations were done daily for 28 days using the oral route. On the 28th day, the rats were exposed to tests that evaluated cognitive function like the hole-board, Morris water maze, and Y-maze test.

Hole board test (modified)

The hole-board test was carried out as expounded by File (1973) with some refining to assess spatial reference memory [12,13]. The apparatus consists of a wooden board (60 cm x 60 cm x 45 cm) with 16 symmetrically spaced holes (5 cm diameter), the board was set at a height of 60 cm from the floor. Spatial reference memory was measured using objects placed permanently as spatial cues. Four of the 16 symmetrically arrayed holes were baited with food pellets. The position of baited holes was fixed for the whole test duration. The food pellets were placed beneath the board to remove olfactory orientation bias. The rats were trained for three days (2 trials per day) from day 25 and a final test on the 28th day, each session beginning 30 minutes post-treatment. Every trial was 20 minutes apart and lasted for 120 seconds. The apparatus was swabbed with 70% alcohol between trials. Visits to baited holes and food pellet removals were noted for each trial. Visits to unbaited holes were recorded as reference memory errors. Reference Memory Index (RMI) which is a measure of the rat's ability to relate with objects in fixed locations was computed as (total visits of baited holes)/ total visits of all holes [13].

Morris water maze test

The Morris water maze expounded by Morris (1984) was utilized to assess the effect of metronidazole treatment on spatial learning in rats [14]. The experiment was performed in a cylindrical vessel, measuring 100 cm by 45 cm, and an elevated platform (6 cm diameter, 29 cm height) was placed in the center of a quadrant of the pool. A non–bioactive dye (starch solution) was used to make the pool opaque to conceal the platform to a depth of 1 cm below the water surface. Objects were placed around the room and on the walls in fixed positions throughout the test period and served as visual cues. Thirty (30) minutes post-treatment, each rat was placed in the water and subjected to two training sessions daily which were 20 minutes apart, for 4 days (the fourth day being day 28) and the timing was after they had found the elevated platform. Any animal that could not seek out the platform in 120

seconds was put on the platform for 10 seconds while animals that found the platform in time were left to stay on it for 10 seconds before removal from the pool. The change in escape latency for the first test represents long-term memory while the difference in escape latency between the first and second tests was recorded as an index of working or short-term memory.

Y-maze test for spatial memory evaluation

The Y-Maze test evaluates the outcome of treatment term short-term memory [15]. The Y-Maze is a wooden frame with three arms (40 x 8 x 15 cm) inclined at an angle of 120° to each other. The arms were labeled A, B, and C. Thirty (30) minutes post-treatment, each rat was introduced to the middle of arm A facing away from the center of the maze and allowed to explore for five (5) minutes. The maze was thereafter cleaned with alcohol to remove odor-induced bias. The number and sequence of arm entries (ABC, BCA, CAB, CBA, BAC, or ACB) were recorded, an entry is noted when all four paws are within the arm. Percentage alternation was calculated as using the formula below [16].

$$Percentage\ Alternations = \left({}^{NA}/_{TAE-2}\right) \times 100$$

Where NA is the number of alternations and TAE is the total arm entries.

Spatial recognition memory on the Y-Maze

A spatial recognition memory test put forward by Sarnyai *et al.* based on the innate proclivity for rodents to search out new areas in their surroundings was carried out in treated rats [17]. Treated rats (30 minutes post-treatment) were placed into an arm (start arm) of the Y maze with one of the arms closed and allowed to explore the maze for 10 minutes (training trial) after which it was returned to its cage. After an hour inter-trial interval, rats were placed on the start arm of the maze and allowed to freely interact with all three open arms for 3 minutes (test trial). Arm entries, dwell time (time spent in the arm) and the arm of first choice entry were recorded. The discrimination ratio which is the inclination of rats for the novel arm over the familiar another arm for arm entry and dwell time was calculated as (Novel/Novel + Other) [18].

Statistical analysis

Results are presented as mean ± standard error of mean (SEM), n is the number of animals per test group. Statistical analysis was done using one-way ANOVA followed by Dunnet's post-hoc test for multiple comparisons (GraphPad prism 6, San Diego, USA). Data were considered significantly different at $p<0.05$.

RESULTS

Metronidazole impairs learning and memory in rats following 28-days oral treatment.

In the hole-board experiment, daily oral treatment with metronidazole for twenty-eight days impaired memory acquisition and learning, and reduced reference memory index (RMI) compared to control ($P<0.05$). Co-administration of metronidazole with risperidone reversed the trend ($P<0.01$) in both the acquisition

phase (day 1-3) and the test phase (day 4) as shown in Figure 1.

In the Morris water maze test for escape latency (Figure 2), the metronidazole treated group took a longer time (P<0.01) to find the escape platform when compared with risperidone for trial 1 and the metronidazole group also took a longer time (P<0.01) to find the platform during trial 2 compared to other treated groups.

Percentage alternation in the Y-maze test was reduced in the metronidazole group (P<0.005) compared to the control and other treatment groups (Table 1). Risperidone alone or co-administered with metronidazole caused a reduction in percentage alternation compared to the metronidazole group (P<0.01).

In the spatial recognition memory test, there was a reduction in visits and time spent in the novel arm than previously visited arms of the Y-maze by the metronidazole treated group compared to other treatment groups and control (P<0.01). However, there was an increase in discrimination ratio for both dwell-time and novel arm entry in the metronidazole + risperidone group compared with the group given metronidazole alone (P<0.05) (Figures 3 and 4). A lower percentage of animals treated with metronidazole also had the novel arm as their first choice of entry compared to other treated groups (Figure 5).

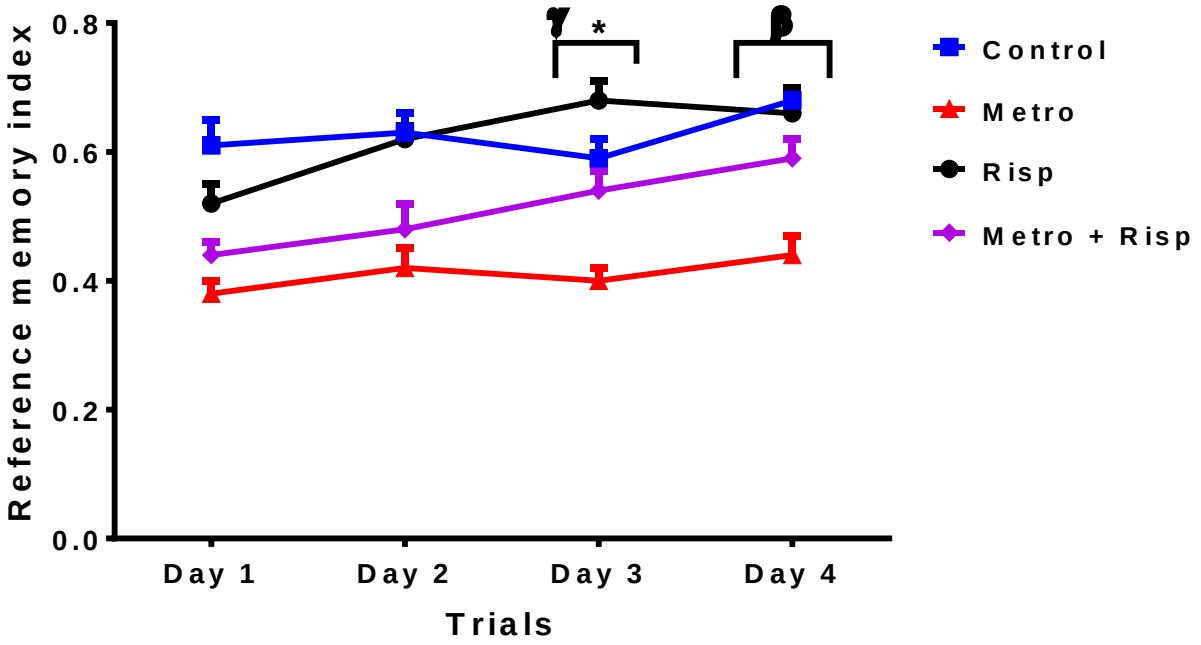

Figure 1: Performance of rats on the hole-board test for spatial recognition memory. Assessment of reference memory index (RMI) following daily oral treatment for 28 days. $^{*}P$<0.05 metronidazole (Metro) only versus metronidazole + risperidone (Risp); metronidazole versus control. $^{\gamma}P$<0.01 metro versus risperidone (day 3), $^{\beta}P$<0.01 metro compared to all groups (day 4). n=5. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), Risperidone (1 mg/kg), metronidazole (50 mg/kg) + risperidone (1 mg/kg).

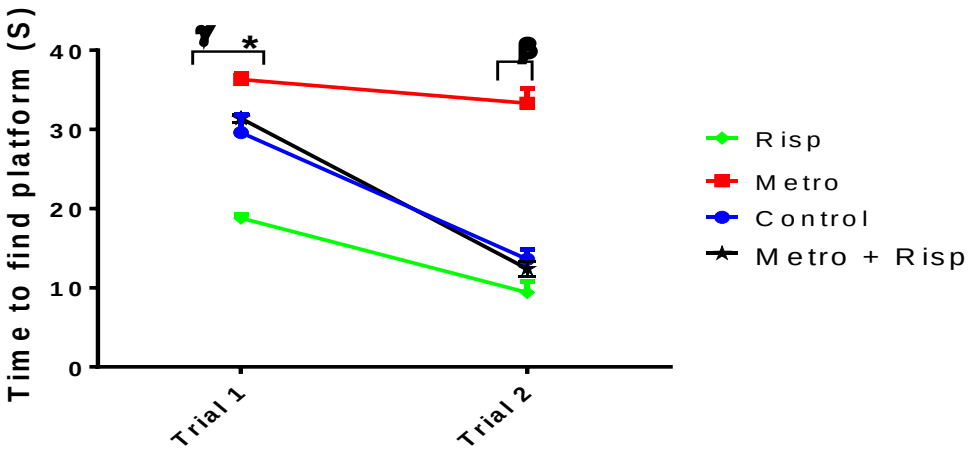

Figure 2: Evaluation of escape latency (working memory) of rats on the Morris water maze after twenty-eight days of treatment with metronidazole. $^{*}P<0.05$ metronidazole (Metro) treated group versus control, $^{\gamma}P<0.01$ metro versus risperidone (Risp) (0 min), $^{\beta}P<0.01$ metro versus all groups (20 min). Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), Risperidone (1 mg/kg), metronidazole (50 mg/kg) + risperidone (1 mg/kg).

Table 1: Evaluation of cognitive function in the Y-maze following 28 days of daily oral treatment with metronidazole.

	Control	Metronidazole	Metronidazole + risperidone	Risperidone
Percentage alternation (%)	68.50 ± 1.26	34.90 ± 1.13**	42.80 $^{\pm}$ 1.90$^{*\pm}$	64. 55 ± 1.65$^{\beta}$

$^{*}P<0.05$, $^{**}P<0.01$ compared to control; $^{\beta}P<0.01$, $^{\pm}P<0.05$ when compared with metronidazole. n=5. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), Risperidone (1 mg/kg), metronidazole (50 mg/kg) + risperidone (1 mg/kg).

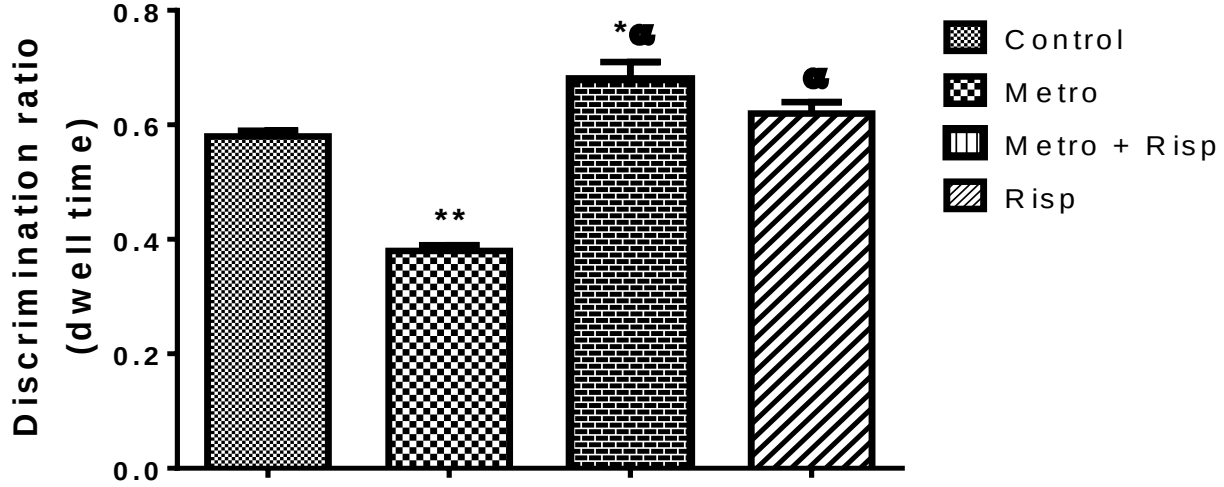

Figure 3: Effect of daily oral treatment (x 28 days) with metronidazole on spatial memory performance on the Y-maze. Discrimination ratio [Preference for the Novel arm over the familiar other arm (Novel/Novel + Other)] for dwell time. $^{*}P<0.05$ versus control, $^{**}P<0.01$ versus control, $^{\alpha}P<0.01$ versus metronidazole alone. n=10. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), Risperidone (1 mg/kg), metronidazole (50 mg/kg) + risperidone (1 mg/kg).

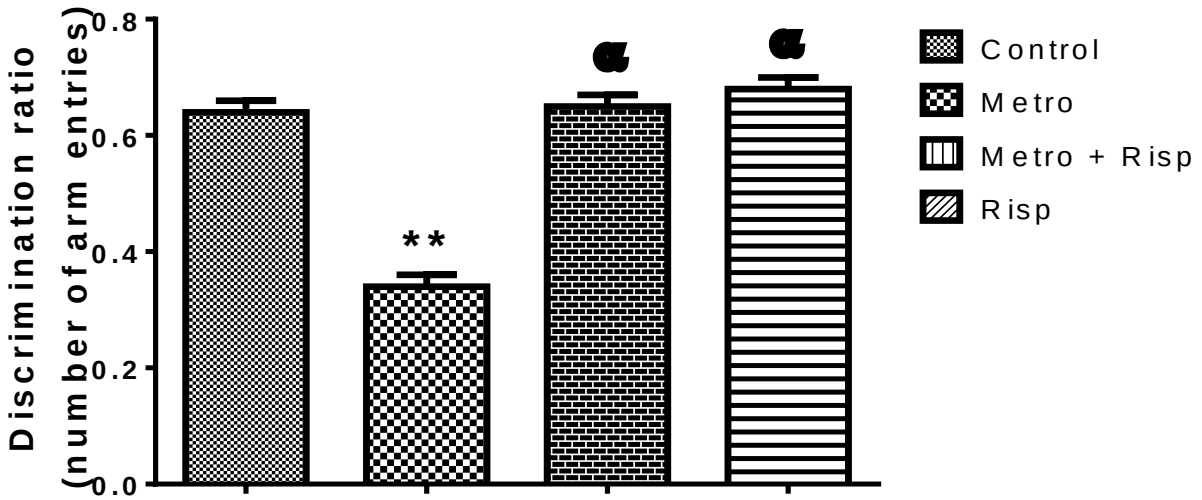

Figure 4: Effect of daily oral treatment (x 28 days) with metronidazole on spatial memory performance on the Y-maze. Discrimination ratio [Preference for the Novel arm over the familiar other arm (Novel/Novel + Other)] for arm entries. $^{*}P<0.05$ versus control, $^{**}P<0.01$ versus control, $^{\alpha}P<0.01$ versus metronidazole alone. n=10. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), Risperidone (1 mg/kg), metronidazole (50 mg/kg) + risperidone (1 mg/kg).

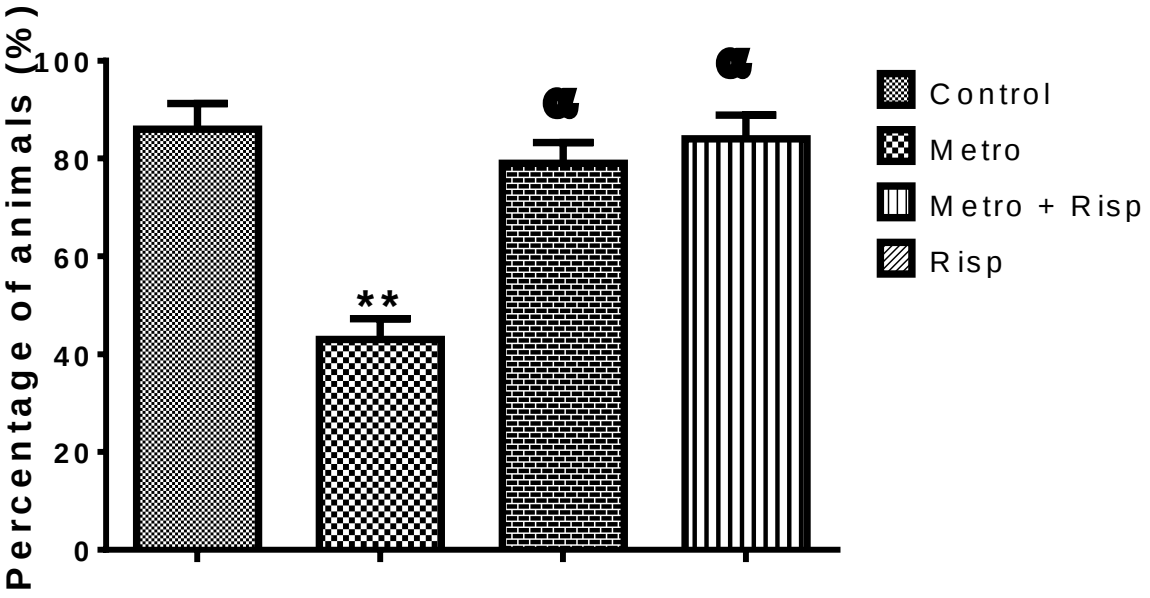

Figure 5: Effect of twenty-eight days oral treatment of rats with metronidazole on the Y-maze. The percentage of animals selecting the novel arm as the first choice 1 h after the first encounter with the partially opened maze (C). $^{*}P<0.05$ versus control, $^{**}P<0.01$ versus control, $^{\alpha}P<0.01$ versus metronidazole. n=10. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), Risperidone (1 mg/kg), metronidazole (50 mg/kg) + risperidone (1 mg/kg).

Discussion

This study demonstrates deficits in learning and memory in rats as one of the manifestations of metronidazole-induced neurotoxicity. Cognitive dysfunction is among the frequently reported symptoms of drug-induced neurotoxicity [4]. It is an array of symptoms arising from iatrogenic processes and includes shortfalls in speech and non-speech learning, attention, short-term and long-term memory [19]. The use of various memory and learning tests has enabled the assessment of cognitive function following prolonged administration of metronidazole in rats.

Metronidzole, a very useful drug in the management of protozoal and anaerobic bacterial infections is reported to induce several neuropsychiatric adverse effects including depression, mania, dizziness, vertigo, headache, and encephalopathy collectively referred to as metronidazole-induced neurotoxicity [20-22]. In this study, metronidazole induced cognitive function deficits in the various cognitive function assessment experiments, however, co-administration with risperidone reversed these effects.

Monoamines are known to regulate cognitive function like emotions, arousal, and memory [23]. The hippocampus thought to be the most central seat for episodic or long-term memory processing, receives multiple neuronal inputs from monoaminergic neurons, including axonal projections from the ventral tegmental area, locus coeruleus, and the dorsal raphe [24]. Furthermore, recent research has reported notable functional associations amongst the cerebellum, prefrontal cortex and hippocampus, these brain structures are known to modulate cardinal cognitive functions encompassing attention and memory, and their malfunction is associated with cognitive deficiencies consistent with neuropsychiatric disorders [25-28]. Cortico-hippocampal neural activity is believed to be controlled by GABAergic inhibition and neural disinhibition in these regions has emerged as a pathophysiological feature in some neuropsychiatric disorders including cognitive dysfunction [29]. Interference with postsynaptic central monoaminergic neurotransmission and modulation of inhibitory neurotransmission are some of the proposed mechanisms of metronidazole-induced neurotoxicity, and these may be contributing factors to the effects seen in this study [30,31].

Dopaminergic neurons implicated in the pathogenesis of Alzheimer's disease are major players in the modulation of cognitive function. Inhibition of central 5-HT_{2A}-receptors is known to stimulate learning and memory improvement, while blockade of D_2-receptors causes memory deficits, in animal models [32,33]. Risperidone, an atypical antipsychotic drug is known to act via antagonism of various receptors including 5-HT_{2A}, 5-HT_1c, dopamine (D_2), and α_2-adrenoceptors in the CNS. Risperidone has a much higher binding affinity on 5-HT_{2A} receptors than it does on the D_2 receptors and is reported to improve learning and memory which is mediated via 5-HT_{2A} receptor antagonism [34]. From our findings in this study, co-administration of metronidazole and risperidone reversed the negative effects of metronidazole on learning and memory

in treated rats. With these findings, it is possible to suggest that metronidazole induces cognitive dysfunction by stimulating 5-HT_{2A} receptors in the CNS. This is in line with a previous study stating that interference with postsynaptic central monoaminergic transmission is a contributory mechanism to metronidazole-induced neurotoxicity [35].

CONCLUSION

Deficits in cognitive function such as learning and memory are symptoms associated with several neurologic diseases, sometimes these deficits may be of iatrogenic origin. This study has demonstrated that metronidazole induces cognitive dysfunction in treated rats and this adds to the spectrum of metronidazole-induced neurotoxicity. In conclusion, it is suggested that metronidazole induces cognitive dysfunction by stimulating 5-HT_{2A} receptors in the CNS, however further studies are required to corroborate these findings.

Abbreviations

RMI: Reference Memory Index; CNS: Central nervous system; 5-HT: 5-hydroxytryptamine; RISP: Risperidone; Metro: Metronidazole; GABA: Gamma aminobutyric acid

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Consent for publication: All authors listed in the manuscript consented to publication.

Author contributions: RIO and BMW conceptualized and designed the experiments. BMW conducted parts of the experiments and conducted the statistical analysis. KI and BMW performed a literature search, conducted the experiments in parts, collected data, and prepared the manuscript in sections. RIO edited the manuscript. BMW, KI, and RIO reviewed the manuscript.

Competing interests: Nil.

Ethical approval: Ethical approval (NDU/PHARM/PCO/AEC/56) was obtained from the institutional animal and ethics committee.

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