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Original Article

Ameliorative effect of allopurinol on cisplatin-induced memory impairment in male Wistar rat

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Abstract

Neurotoxicity is an adverse effect of chemotherapy drugs on the central nervous system. Many studies have demonstrated that xanthine oxidase inhibitors prevent the formation of reactive oxygen species (ROS). The present study aimed to investigate the effects of allopurinol as an oxidase inhibitor on the learning and memory impairment induced by cisplatin. This study was conducted on 40 male Wistar rats, which were randomly divided into five groups, as follows: 1) control injected with saline (1 ml/kg/i.p); 2) cisplatin (5 mg/kg/once a week; i.p.); 3) allopurinol (ALP; 50 mg/kg/once a week; P.O.); 4) Cis+ALP 50 (cisplatin 5 mg/kg/i.p and allopurinol50 mg/kg/once a week; P.O.) and 5) Cis+ALP 100 (cisplatin 5 mg/kg/i.p and allopurinol100 mg/kg/once a week; P.O.). Drugs were administered for five weeks in all groups. The interval between administrations of drugs were half an hour. Morris water maze (MWM) was used to evaluate the memory and learning of the animals. The tissue brain concentrations of malondialdehyde (MDA), thiol, and superoxide dismutase (SOD) were measured using biochemical tests. According to the results, the cisplatin group had longer escape latency and shorter time spent and traveled pathway in the target quadrant compared to the control group. On the other hand, allopurinol treatment significantly reversed the results of the spatial memory test. The biochemical data indicated that cisplatin increased MDA concentration but decreased thiol and SOD activity compared to the control group. Administration of allopurinol decreased the MDA level but increased the thiol levels in the cortex and hippocampus tissues. Therefore, it was concluded that allopurinol could improve cisplatin-induced memory impairment by affecting the oxidative status of the brain tissue.

*Keywords***:** Allopurinol, Cisplatin, Memory, Malondialdehyde, Thiol, Superoxide dismutase.

1. Introduction

Chemotherapy is an effective treatment to prevent the growth and division of cancer cells, while it is associated with multiple complications, such as nervous system involvement. To date, researchers have explored the environmental effects of chemotherapy on the nervous system, confirming complications such as neuropathic pain [1]. Recently, scientists have focused on the cognitive impairment induced by chemotherapy [2-4].

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Cisplatin is a chemotherapy drug used for the treatment of numerous human cancers, such as sarcomas and musculoskeletal cancer [5-7]. Cisplatin stimulates cell apoptosis and causes DNA damage. Furthermore, the accumulation of cisplatin in the tissues leads to several substantial toxicities, including nephrotoxicity, cardiotoxicity, gastrotoxicity, and neurotoxicity [8-11]. Reactive oxygen species (ROS), oxidative stress, and decreased levels of antioxidant enzymes are considered to be the major alterations in cisplatin-induced toxicity [12]. Inflammation, neurogenesis inhibition, and apoptosis promotion leading to neural damage have also been reported as the side-effects of cisplatin on the nervous system [13].

For decades, allopurinol has been used as a major drug for the treatment of gout, recurrence of calcium oxalate kidney stones, and nephropathy in the course of chemotherapy [14-17]. Allopurinol inhibits the xanthine oxidase enzyme, which produces uric acid in the human body, thereby reducing uric acid levels. Previous studies have shown that in some pathological conditions, allopurinol exerts therapeutic effects by reducing oxidative stress [18-20]. For instance, Safari et al. confirmed the anti-nociceptive effects of allopurinol on a neuropathic pain model [7]. Allopurinol could also penetrate the brain and improve its function by reducing the inflammation status [20], and the beneficial effects of allopurinol on acute ischemic stroke have been documented [21]. Some studies pointe to the role of oxidative stress from lipid peroxidation and ROS in disrupting the central nervous system [4]. The hippocampus and its function in memory is significantly impacted by oxidative stress situation [13].

Recent findings in this regard have indicated that allopurinol could decrease the neuronal damage caused by oxidative stress [22-25].

Although many studies have looked at the different effects of allopurinol, few studies have done on the effect of this drug on cognition. The present study aimed to determine whether allopurinol could improve the memory function in cisplatin-induced memory impairment and we sought to investigate possible mechanism by measuring levels of oxidant and anti-oxidant markers in the rat's brains.

2. Materials and Methods

2.1. Animals and Drugs

This study was conducted on 40 male Wistar rats aged eight weeks (weight: 250±10 g). The animals were housed in standard cages (4 per each) at room temperature (23-25°C) at the proper humidity and within a 12-hour light/dark cycle (light at 7:00 AM). The behavioral studies were performed at the same time of the day (11 AM-4 PM). All the experiments were performed in accordance with the Ethics Committee Guidelines for Research on Laboratory Animals of Sabzevar University of Medical Sciences (IR.MEDSAB.RES.1398.032). Cisplatin (EBEWE Pharma Ges.m.b.h, Austria) and allopurinol (Temad Ltd., Tehran, Iran) were Kused in the current research.

2.2. Experimental Groups

The animals were randomly divided into five groups of eight. The rats of group one (control) had free access to normal food and water. Group two received intraperitoneal cisplatin (5 mg/kg) once per week for five

weeks [26], group three received allopurinol (50 mg/kg) via oral gavage daily for five weeks [27]. groups four and five were administered with intraperitoneal cisplatin (5 mg/kg) and allopurinol (50 and 100 mg/kg/ P.O) for five weeks. Behavioral tests were performed on all the study groups for six consecutive days at the end of the experiments.

2.3. Behavioral Tests

Morris water maze (MWM) is a circular tank with a diameter and height of 150 and 60 centimeters, respectively [28]. In our study, a platform with a diameter of 10 centimeters and height of 28 centimeters was centered in one of the four quadrants. The tank was filled with water to the height of 30 centimeters (temperature: 23-25°C), and the platform was submerged to two centimeters below the water surface so that it would be invisible at the water level. The experimenters and computer/visible cues remained constant throughout the tests [29, 30].

Before the experiments, the animals were allowed to swim in the tank for 60 seconds without a platform. The experiments were carried out in four trials for five days and two trials on the sixth day. The platform was removed on the sixth day, and the tests were performed afterwards. In each trial, the animals were in the pool facing the tank wall and swam to find the platform. The animals were allowed to stand on the platform for 20 seconds; if they could not find the platform within 60 seconds, they were placed on the platform for another 20 seconds. The swimming distance, time latency to find the platform, and speed were recorded automatically by a video tracking system [31].

2.4. Biochemical Analysis

2.4.1. Malondialdehyde Measurement

At the end of the behavioral experiments, the animals were deeply anesthetized and sacrificed. Afterwards, tissue samples were collected and exposed to the temperature of -80°C until the biochemical analysis was performed. The samples were weighed and homogenized with Phosphate-buffered saline, and the malondialdehyde (MDA) level was measured manually. To do so, one milliliter of the homogenate brain (hippocampus and cortex) sample was mixed with two milliliters of thiobarbituric acid and trichloroacetic acid, and the mixture was incubated in a hot water bath (100°C) for 10 minutes. Finally, the absorbance was read at 532 nanometers using a spectrophotometer [32].

2.4.2. Thiol and SOD Measurement

To measure the thiol content (hippocampus and cortex), a mixture of ethylenediaminetetraacetic acid (EDTA)-Tris buffer was added to 50 milliliters of the tissue samples at the pH of 8.6, and the absorbance was read at 412 nanometers. Following that, 0.02 milliliter of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) was added to the mixture, and the samples were incubated at room temperature for 15 minutes. The absorbance of the samples was read again, and the absorbance of DTNB was considered blank. In addition, the thiol level was measured at 535 nanometers. Superoxide dismutase (SOD) activity was also determined using the method proposed by Madesh and Balasubramanian and measured at 570 nanometers [33].

2.5. Statistical Analysis

Data analysis was performed in SPSS using one-way analysis of variance (ANOVA) followed by the LSD post-hoc comparison test. The obtained values were expressed as mean and the standard error of the mean (SEM). Moreover, repeated measures ANOVA was used for the MWM escape latency analysis. In all the statistical analyses, the P-value of less than 0.05 was considered significant.

3. Results and Discussion

The effects of allopurinol on the memory impairment induced by cisplatin were evaluated using the MWM. According to the findings, the mean latency gradually decreased during the behavioral tests in all the experimental groups. On the other hand, the animals treated by cisplatin took longer to access the platform compared to the control group ($P<0.05$ and $P<0.001$, respectively) (Fig. 1a). The administration of allopurinol also reduced the escape latency in all the groups receiving allopurinol compared to the cisplatin group ($P<0.05$ and $P<0.001$, respectively) (Fig. 1a).

In the probe trial test (day six), the time spent and distance traveled in the target quadrant were calculated to evaluate spatial learning and memory enhancement. According to the obtained results, the cisplatin-treated animals had a lower percentage of the time spent and distance traveled compared to the control group ($P<0.05$) (Fig. 1b, 1c). Furthermore, the animals receiving allopurinol and allopurinol (100 mg/kg) plus cisplatin showed significant differences and a higher percentage of the time spent and distance traveled in the target quadrant (Fig. 1b, 1c). The swimming speed of the cisplatin group was lower than the control group, while it was higher in the groups receiving allopurinol compared to the cisplatin group (Fig.1d).

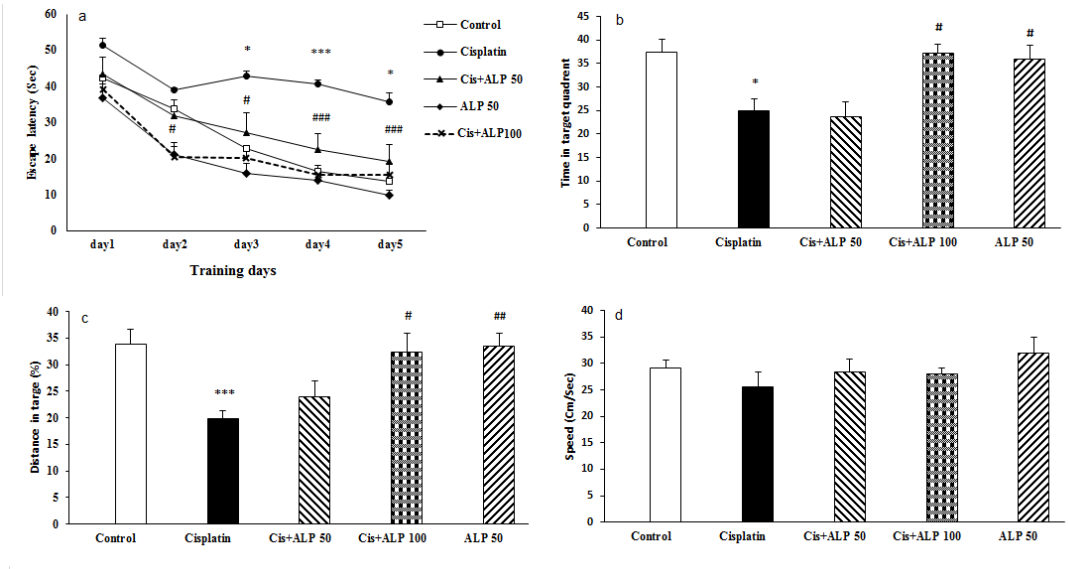

Figure 1. Comparison of the time latency (a), percentage of time spent (b), percentage of traveled distance (c) and swim speed (c) in the target quadrant in MWM test between groups. The data are expressed as the Means ± SEM.***$p < 0.001$ and *$p < 0.05$ compared to control group, ###$p < 0.001$ and #$p < 0.05$ compared to cisplatin group ($n = 8$).

The results of lipid peroxidation in the present study indicated that cisplatin treatment significantly increased the MDA levels of the brain tissue (P<0.001) compared to the control group (Fig. 2a, 2b). On the other hand, allopurinol administration significantly decreased the MDA levels of the hippocampus tissue (P<0.01) (Fig. 2a), while treatment with allopurinol ameliorated the MDA levels of the cortex tissues (P<001) (Fig. 2b).

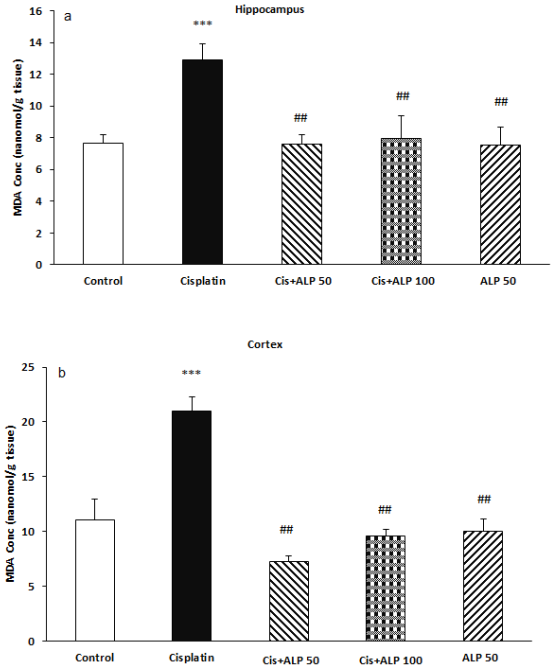

Figure 2. Effect of allopurinol and cisplatin on hippocampus (a) and cortex MDA level (b). Data are express as Mean ± SEM. ***p < 0.001 compared to control group, ##p < 0.01 compared to cisplatin group (n = 8).

According to the findings, thiol production significantly decreased in the brains of the cisplatin-treated group (P<0.05) (Fig. 3a, 3b). On the other hand, the administration of allopurinol (50 and 100 mg/kg) significantly increased the thiol levels of the hippocampal tissues compared to the cisplatin-treated group (P<0.05 and P<0.001, respectively) (Fig. 3a). Furthermore, the thiol levels of the cortex tissues were significantly higher in the allopurinol treatment groups compared to the cisplatin group (P<0.05 and P<0.001, respectively) (Fig. 3b).

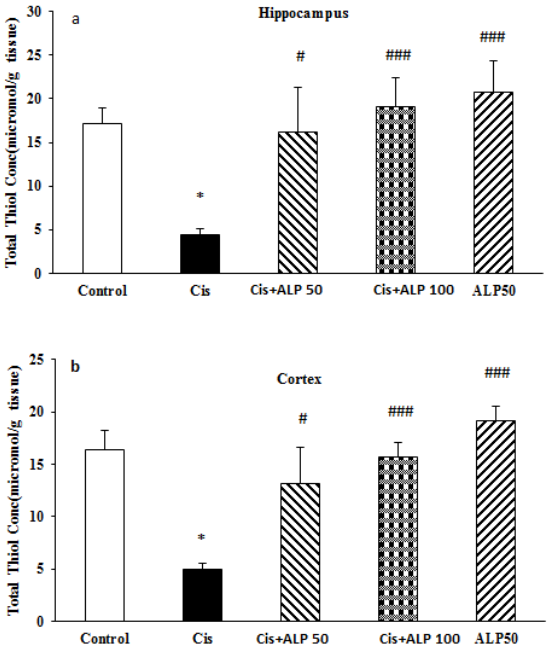

Figure 3. Effect of allopurinol and cisplatin on hippocampus (a) and cortex total thiol level (b). Data are express as Mean ± SEM. *p < 0.05 compared to control group, ###p < 0.001 and #p < 0.05 compared to cisplatin group (n = 8).

The assessment of the brain tissues indicated a significant decrease in the SOD activity of the cisplatin treatment group compared to the controls (P<0.05) (Fig 4a, 4b). On the other hand, the SOD activity in the hippocampus and cortex tissues increased following administration of allopurinol (50 and 100 mg/kg), while it was not considered significant (Fig. 4a, 4b). However, no significant difference was observed between the two doses of allopurinol in this regard (Fig. 4a, 4b).

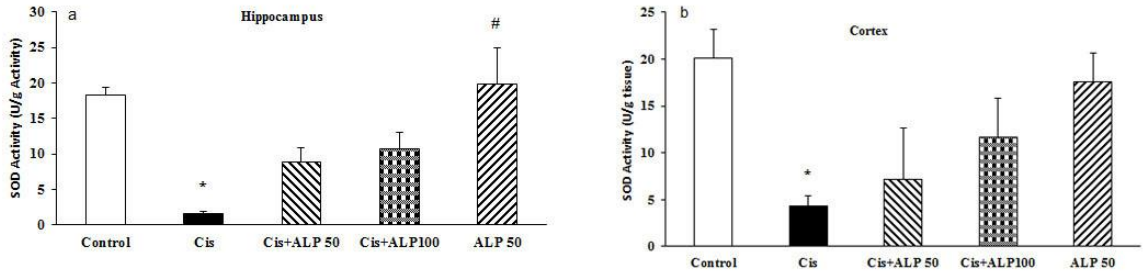

Figure 4. Effect of allopurinol and cisplatin on hippocampus (a) and cortex SOD level (b). Data are express as Mean ± SEM. *p < 0.05 compared to control group, #p < 0.05 compared to cisplatin group (n = 8).

The present study aimed to evaluate the effects of allopurinol on the cognition impairment induced by cisplatin as an anticancer drug in male rats. According to the obtained results, cisplatin administration for five weeks significantly increased the escape latency time in the training trials. In the probe trial test, the distance and time in the target quadrant decreased in the cisplatin-treated rats, which is in line with the previous studies in this regard [26, 34, 35].

Behavioral studies have confirmed that cisplatin impairs memory and learning [27, 31]. As an anticancer drug, cisplatin has various side-effects, including hepatotoxicity [36], nephrotoxicity [37], ototoxicity [38], and neurotoxicity [26, 39]. In addition to its peripheral effects, cisplatin could also affect the central nervous system. Evidence suggests that cisplatin cannot easily cross the blood-brain barrier (BBB) in normal physiological conditions [26], while it crosses the BBB under specific conditions, such as short-term hypoxia [40]. Furthermore, the study of Purkinje cells in the cerebellum has shown that cisplatin crossing the BBB could destroy these cells [41].

According to the literature, cisplatin binds to special proteins that enable them to cross the BBB [42], while some findings attribute this phenomenon to the structural changes in the BBB capillaries [41]. Cisplatin accumulates in target cells and causes the overproduction of ROS, which could disrupt the physiological balance of the cells [39]. Our findings indicated that the biochemistry markers of MDA, thiol, and SOD in the brain changed after cisplatin treatment. The levels of thiol and SOD (antioxidant markers) decreased, while the MDA level (lipid peroxidation marker) increased. Previous studies have investigated the involvement of oxidative stress in cisplatin-induced cognitive impairment [26, 35].

According to the study by Jangra et al., cisplatin treatment could cause memory and learning impairment by affecting lipid oxidation and reducing the levels of antioxidants in the brain [43]. Endogenous antioxidant enzymes (e.g., thiol and SOD) and other molecules are effective in scavenging the augmentation of the ROS generated in the brain and other tissues [44]. Our study revealed that the combination of allopurinol and cisplatin could improve the spatial memory of the cisplatin treatment rats, while also moderating lipid peroxidation in the hippocampus and cortex tissues. These findings are consistent

with the study by Mehmet Oz et al., in which curcumin (another antioxidant) was used against cisplatin-induced learning and memory impairment [26]. Memory and learning improvement after antioxidant therapy has also been confirmed in other models of memory impairment in the previous studies [45-47]. In an *in-vivo* study, antioxidants were reported to cause neurogenesis and plasticity in the hippocampus [48-50].

According to the literature, allopurinol as a xanthine oxidase inhibitor has antioxidant properties, which could reduce the concentration of the biological markers of oxidative stress in humans [51]. Moreover, allopurinol has been shown to decrease the production of ROS through direct and indirect effects [52]. Some authors argue that the beneficial effects of allopurinol are mediated by the uric acid-lowering effects of this drug, which limit the toxic overproduction of ROS [53, 54]. Allopurinol inhibits purine metabolism and reduces the formation of uric acid by inhibiting the xanthine oxidase enzyme [55].

Hyperuricemia causes oxidative stress in patients with gout. After the administration of allopurinol to these patients, serum MDA levels were observed to decrease [56]. Furthermore, allopurinol is a scavenger of free radicals through the production of hydroxyl radical and superoxide anion [56], and this effect has been documented in studies regarding ischemic reperfusion [57-59]. However, some studies have reported that allopurinol is not able to inhibit cisplatin-induced lipid peroxidation in the kidneys [60, 61]. The preventive effects of allopurinol against lipid peroxidation in cerebral and hepatic tissues have also been confirmed by Belma Giray et al. [62]. The research by Rodríguez-Fanjul et al. demonstrated the beneficial effects of allopurinol on behavior following morphological changes in the hippocampus and cerebral cortex of animals [21].

The current research had some limitations. Despite the memory improvement and increased levels of antioxidants in the brain of the rats in the present study, histological and molecular studies are required to observe the cellular changes resulting from the nuclear and mitochondrial DNA damages in the hippocampus. Another limitation of our study was that the concentration of cisplatin in the brain was not measured.

4. Conclusion

We investigated the effects of allopurinol on cisplatin-induced learning and memory impairment. According to the results, allopurinol improved cognitive decline by restoring the lipid peroxidation and antioxidant concentrations in the hippocampus. Therefore, it could be concluded that allopurinol may be used for neuroprotection in chemotherapy protocols.

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