Research article

Olanzapine attenuates postoperative cognitive dysfunction in adult rats

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ABSTRACT

Background: Postoperative cognitive dysfunction (POCD) is associated with poor quality of life and difficulty working. Its impact may be greater in middle-aged patients than in elderly patients. Neuroinflammation is reported to be a main cause of POCD. Olanzapine has been reported to improve learning and memory functions. We therefore investigated olanzapine's effectiveness and mechanisms in an adult rat POCD model.
Methods: Six-month-old rats underwent laparotomy and lipopolysaccharide (LPS group) or LPS + olanzapine (OLA group) intraperitoneal injection or anesthesia alone (CON group) 1 week after a Barnes maze training session. A Barnes maze test trial was then conducted the day after surgery or anesthesia. The microglial activity in the hippocampus and cytokine levels were measured by Iba1 staining and enzyme-linked immunosorbent assay, respectively.
Results: The OLA group had significantly higher success rates of Barnes maze trial than the LPS group. The success rate in time of the OLA group was inferior to that of the CON group. On the other hand, the success rate in distance of the OLA group was similar to that of the CON group. Iba1 staining areas in the LPS and OLA groups were larger than that in the CON group; however, the staining area in the OLA group was smaller than that of the LPS group. Plasma interleukin-1β concentration in the LPS and OLA groups was significantly higher than that in the CON group; however, there was no significant difference between the LPS and OLA groups.
Conclusion: Olanzapine attenuated both spatial cognitive dysfunction and microglial activity of the hippocampus, which were induced by surgery and LPS injection. These effects were unrelated to inflammatory cytokine concentrations in plasma and hippocampus.

1. Introduction

The morbidity of postoperative cognitive dysfunction (POCD) in patients between 40 and 60 years of age is reported to be 19.2% seven days and 6.2% three months after major noncardiac surgery [1]. Long-term POCD might delay patients' rehabilitation, increase their risk of complications, postpone hospital discharge and their return to work, increase their hospitalization cost, and deteriorate their quality of life (including giving up work and social activities) [2, 3].

Neuroinflammation is one of the main causes of POCD. After surgery, many cytokines are released from the injured tissue. The cytokines damage the blood-brain barrier and activate microglia. Activated microglia release cytokines, which can damage neurons and recruit other inflammatory cells from the blood. The recruited inflammatory cells also release cytokines and activate microglia further. This neuroinflammation

network is speculated to aggravate neural damage and lead to POCD [4, 5].

Olanzapine is a safe atypical antipsychotic that rarely causes severe extrapyramidal symptoms. It is widely used to treat schizophrenia, bipolar disorder, and other psychoses [6, 7, 8]. Immediately after the start of its clinical use, olanzapine was shown to improve cognitive functions in patients with schizophrenia [9]. Subsequent clinical observations have also indicated that olanzapine benefits memory functions [10, 11]. Furthermore, experimental studies have shown that olanzapine improved memory functions and prevented cognitive disorders in both rodent models of schizophrenia and normal rats [12, 13, 14, 15].

Larsen et al. [16] reported that olanzapine decreased the incidence of postoperative delirium in elderly patients with joint replacements. However, to the best of our knowledge, few studies have investigated the effects of olanzapine and its mechanisms on cognitive dysfunction after

surgery. The present study was designed to evaluate the effects of olanzapine in an adult rat POCD model. Furthermore, we investigated the relationship between olanzapine and neuroinflammation.

2. Materials and methods

The present study was approved by the Institutional Animal Care and Use Committee of the University of Tsukuba and was performed in accordance with guideline of the Japanese Association of Laboratory Animal Facilities of National University Corporations. Sixty-three 6-month-old male Sprague Dawley rats were purchased from Japan SLC, Inc. (Hamamatsu, Shizuoka, Japan). 36, 12, and 15 rats were used for behavioral, histopathological, and cytokine measurement studies, respectively (Figure 1). The 36 behavioral study rats were randomly allocated to three groups (12 rats per group): 1) isoflurane anesthesia without surgery (control: CON group), 2) laparotomy and administration of lipopolysaccharide (LPS) (0.1 mg/kg) and normal saline (1 ml/kg) (LPS + normal saline: LPS group), or 3) laparotomy and administration of LPS (0.1 mg/kg) + olanzapine (0.1 mg/kg) (LPS + olanzapine: OLA group). The 12 histopathological study rats were allocated to the CON group (n = 2), LPS group (LPS 1 mg/kg + normal saline 1 ml/kg) (n = 5), or OLA group (LPS 1 mg/kg + olanzapine 1 mg/kg) (n = 5). The 15 cytokine measurement study rats were allocated to the CON group (n = 5), LPS group (LPS 1 mg/kg + normal saline 1 ml/kg) (n = 5), or OLA group (LPS 1 mg/kg + olanzapine 1 mg/kg) (n = 5). In the behavior test, LPS and olanzapine were used 1/10 dose of the histopathological and cytokines measurement studies, because high doses did not allow observation of rat behavior due to drowsiness.

2.1. LPS and olanzapine

LPS from *Escherichia coli* strain 0111:B4 (L2630; Sigma-Aldrich, St. Louis, MO, USA) [17] and olanzapine (Eli Lilly & Company, Indianapolis, IN, USA) were administered intraperitoneally just before closing the laparotomy. LPS and olanzapine were dissolved in 0.9% NaCl (pH 7.4) and administered in volumes of 0.5 ml/kg and 1 ml/kg, respectively.

2.2. Barnes maze training

The Barnes maze consisted of a circular gray platform with a diameter of 120 cm that was elevated 65 cm from the floor and included 20 equally spaced holes (10 cm in diameter) in the periphery (Muromachi Kikai Co., Ltd., Tokyo, Japan). One of the holes was connected to an escape box (22 cm × 13 cm × 13 cm) of the same material and color as the platform. The other holes were covered underneath with a flat board, also of the same material and color. The light of the room was 160 W.

One week before surgery, the rats underwent 10 Barnes maze training sessions in a manner previously described [18]. After the rats were acclimated to the testing suite (1 h), they were taken to the testing room in their home cages. Training began by placing each rat in the start box, which was located at the center of the maze, one at a time. After 10 s, the start box was lifted away, and noise (about 90 dB) was made to urge the rat. The rat was given 180 s to explore. Upon entering the escape box, the rat was allowed to stay undisturbed for 2 min. If the rat failed to find the escape box within 180 s, it was gently guided into the escape box and allowed to remain for 2 min. The rat was then returned to its home cage for a 15-min intertrial interval. This training process was then repeated 9 times. All training processes were recorded using a camera connected to a computer (NEC, Tokyo, Japan), and the data were analyzed using the ANY-maze software (Stoelting Co., Wood Dale, IL, USA). Maze and escape box surfaces were cleaned with ethanol between each trial to minimize olfactory cues.

2.3. Surgery

The rats were anesthetized with 2% isoflurane on room air. After body weight, body temperature, and blood glucose level (Accu-Chek; Roche DC Japan Co., Tokyo, Japan) were measured, a laparotomy was performed following the methods reported in a previous study [19]. A 3-cm longitudinal midline incision was made 0.5 cm below the sternum. The intestines were pulled out of the abdominal cavity and rubbed for 5 min. After the intestines were returned to the abdominal cavity, LPS and olanzapine were injected in the cavity, and the abdominal muscle and skin were sutured. The control rats only underwent isoflurane anesthesia and body weight, body temperature, and blood glucose level measurements.

2.4. Behavioral evaluation

2.4.1. Open field study

The day after surgery, the rats' locomotor activity and behavior in an open field were evaluated. The open field apparatus consisted of a wooden square box (60 cm × 60 cm × 40 cm), to which the rats had not previously been exposed. Each rat was placed in turn into the center of the arena, and its spontaneous locomotor activity, rear-up frequency, and grooming actions were recorded for 5 min. The data were analyzed using the above-mentioned video-tracking system.

2.5. Barnes maze

After the open field study, each rat underwent Barnes maze test trials separated by a period of more than 15 min. Since the rats sometimes
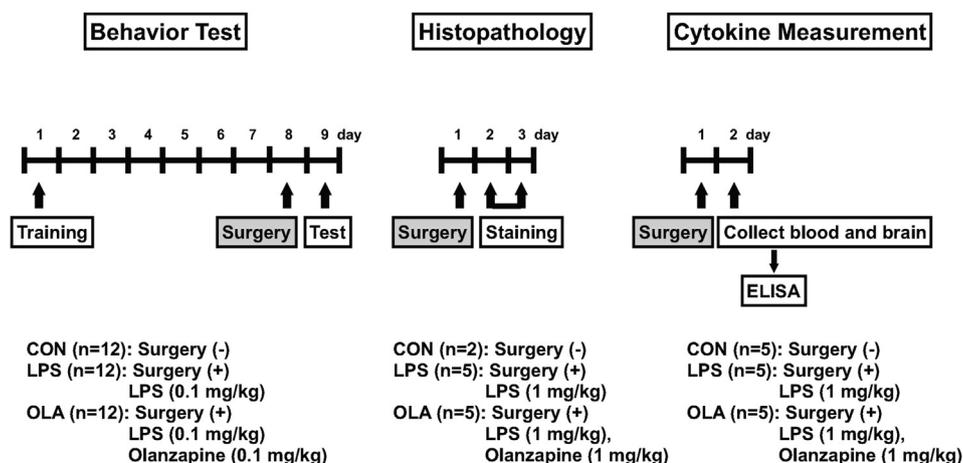
Figure 1. Protocol design and timeline of each sub-study. ELISA: enzyme linked immunosorbent assay.

arrived at the goal coincidentally, the test was conducted three times in each rat. During the training phase, 90% of the rats identified the escape box within 20 s and 2.2 m by the last trial (Figure 2). Thus, 20 s and 2.2 m were used as criteria of cognitive function with reference to a previous report [20]. Traditionally, learning in the Barnes maze is assessed by the time and distance required to enter the escape box. However, it has been observed that rats sometimes stay beside the escape box or continue exploring the maze after learning the positional relationship between the room view and escape box. Thus, we recorded the time and distance it took for the rats to first identify the escape box, as previously reported [21].

2.6. Histopathological evaluation

The day after surgery, the rats were deeply anesthetized with intraperitoneal pentobarbital (150 mg/kg) and killed after body temperature and blood glucose level were measured. The rats were perfused through the ascending aorta with 500 ml of phosphate-buffered saline (PBS) followed by 500 ml of 4% paraformaldehyde fixative in a 0.1 M phosphate buffer. After perfusion, the brain was removed and postfixed in the same fixative for 2 h at 4 °C, after which it was cryoprotected in 20% glycerol in a 0.1 M phosphate buffer. Cross sections involving the hippocampus were cut at a 40-μm thickness using a cryostat.

After washing with 0.05 M PBS, the sections were incubated in a blocking solution of 0.05 M PBS with 0.3% peroxidase and 0.2% Triton-X (Sigma-Aldrich) for 30 min at room temperature. The sections were then incubated in primary antibody solution (rabbit anti-Iba1, 1:10000; FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) overnight at 4 °C. On the second day, these sections were washed with 0.05 M PBS twice and then processed according to the usual protocol of the avidin-biotin-peroxidase method (VECTASTAIN ABC-HRP Kit; Vector Laboratories, Burlingame, CA, USA), with diaminobenzidine hydrochloride as a chromogen. Every section was reacted for the same period and with the same reagents.

Figure 2. Learning performance during the Barnes maze training phase. A) Time: time until first identification of the escape box. B) Distance: walking distance until the first identification of the escape box. By the 10th session, the time and distance of 90% of the rats was less than 20 s and 2.2 m, respectively. Results are expressed as medians (10th and 90th percentiles).

When microglia are activated, the cell body enlarges and the processes contract and thicken [22]. The activity of microglia was estimated by measuring the rate of stained area of Iba-1 to surface area [23, 24]. Photographs of each section were taken and analyzed using an exclusive software (All-in-One Fluorescence Microscope BZ-X710 and BZ-X-Analyzer; KEYENCE Corporation, Osaka, Japan). The Iba1-staining area was analyzed at 24 spots of hippocampus each rats.

2.7. Enzyme-linked immunosorbent assay (ELISA)

Blood samples were taken from 15 rats, which were decapitated under isoflurane and pentobarbital anesthesia the day after surgery. The blood samples were anticoagulated with ethylenediaminetetraacetic acid and centrifuged at 1000 G. The isolated hippocampus was homogenized in neuronal protein extraction reagent buffer (Thermo Fisher Scientific, Waltham, MA, USA) containing protease inhibitor (ThemoFisher Scientific). After homogenization, the lysates were centrifuged at 100 G. Tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) levels were determined using ELISA kits specific for rat TNF-α and IL-1β (R&D Systems, Inc., Minneapolis, MA, USA) according to the manufacturer's instructions. The absorbance values were measured at 450 nm and 540 nm using a micrometer plate reader.

2.8. Statistical analysis

Data collected from the Barnes maze trials were analyzed using a chi-squared test. All other data were analyzed with a Kruskal-Wallis test. Since the data did not show normal distribution, the Steel-Dwass test was used to identify which group differences accounted for the significant p value [25]. Statistical significance was set at < 0.05.

3. Results

There was no significant difference in preoperative body temperature between the three groups. The postoperative body temperature in the LPS and OLA groups was significantly higher than that in the CON group. There was also no significant difference in blood glucose level between the three groups (Table 1).

The LPS and OLA groups showed shorter distance and slower speed than the CON group in the open field study; however, there was no significant difference between the LPS and OLA groups. The number of rear-ups in the OLA group was lower than that of the CON group. There was no significant difference among the three groups in the number of rats that began grooming actions during the observation period (Table 1).

The success rate of escape box identification during the Barnes maze test (that is, the preoperative cognitive function criteria pertaining to both time and distance were met) was significantly higher in the OLA group than in the LPS group. The success rate in time of the OLA group was inferior to that of the CON group. On the other hand, there was no significant difference in the success rate in distance between the OLA group and the CON group (Figure 3).

The percentage of Iba1-staining area in the LPS and OLA groups was significantly higher than that in the CON group in all regions of the hippocampus. However, the percentage of Iba1-staining area in the OLA group was lower than that in the LPS group. Figure 4 shows the results of the cornu ammonis 2 (CA2) area. The same results were observed in the cornu ammonis 1 area, cornu ammonis 3 area, and dentate gyrus (data not shown).

The plasma IL-1β concentration in the LPS and OLA groups was significantly higher than that in the CON group; there was no significant difference between the LPS and OLA groups. No significant differences in hippocampal IL-1β concentration were found between the three groups (Figure 5). The plasma and hippocampal TNF-α concentrations were very low; there were no significant differences in TNF-α concentration between the three groups (data not shown).

Table 1. Results of body temperature, blood glucose, and open field.

	Control	LPS	LPS + Olanza
Body Temperature (ºC)			
Pre-surgery	36.6 ± 0.5	36.5 ± 0.3	36.6 ± 0.3
Post-surgery	38.2 ± 0.3	38.7 ± 0.2*	38.6 ± 0.4*
Blood Glucose (mg/dl)			
Pre-surgery	132 ± 20	137 ± 17	123 ± 20
Post-surgery	-	146 ± 27	129 ± 16
Next day	95 ± 7	100 ± 12	102 ± 9
Open Field			
Central Zone (s)	27 ± 16	16 ± 8	29 ± 43
Distance (m)	7.1 ± 3.0	4.9 ± 2.3	3.7 ± 3.9*
Speed (cm/s)	9.9 ± 0.9	8.7 ± 1.2*	8.0 ± 1.4*
Rear-Up	12.2 ± 6.4	7.7 ± 4.9	5.3 ± 3.5*
Grooming (+/-)	11/1	7/5	9/3

* vs Control, mean ± SD.

4. Discussion

We investigated the effects of olanzapine in an adult rat POCD model. Barnes maze results demonstrated that olanzapine attenuated spatial cognitive dysfunction. Olanzapine inhibited microglial activity in the hippocampus, but it did not inhibit plasma IL-1β concentration increases.

It is difficult to create a long-term cognitive dysfunction model in 6-month-old rats [26]. The cognitive function of adult rats is frequently ameliorated in a few days. However, large-scale surgery with LPS injection was shown to cause severe cognitive dysfunction and increased mortality in the rats in our preliminary study. The Barnes maze enabled us to investigate rats' cognitive function with less physical and mental stress than a water maze, as the Barnes maze is a dry maze, so its completion is motivated only by a rodent's indigenous agoraphobia [21]. Given that the short study period and use of the Barnes maze lightened the burden on the rats in the present study, it was possible to do large-scale surgery with LPS injection.

For 90% of the rats in this study, the time and distance until identification of the escape box decreased to 20 s and 2.2 m, respectively, after 10 training sessions. These results were in accordance with other report [27]. The present study showed that the time taken to identify the escape box in the CON group was less than that of the other groups. However, the speed of the LPS and OLA groups was likely slower than that of the CON group due to the abdominal surgery. To assess memory function precisely, it is suitable to evaluate distance rather than time. The distance

taken until escape box identification in the OLA group was similar to that of the CON group. The OLA group demonstrated shorter distance than the LPS group, despite both groups undergoing the same surgery. This result could be interpreted as showing the effect of olanzapine on POCD.

The rear-up frequency of the OLA group was lower than that of the CON group in the open field, which was new to each rat; this may indicate that olanzapine helps to retain the memory of, but decreases the curiosity about, a new object. Thus, a novel object recognition test might be inadequate for evaluating the effects of olanzapine.

It is well-known that olanzapine induces hyperglycemia [28]. Perioperative hyperglycemia may be associated with an increased risk for POCD [29]. Zhang et al. [30] reported that hyperglycemia could augment LPS-induced microglial activation and inflammatory cytokine levels. In the present study, however, hyperglycemia was not observed in the OLA group; this may be because natural fasting due to the abdominal surgery negated the depressive effect of olanzapine on insulin secretion.

The body temperature of the CON group was increased on the second day in the present study, which may be due to the conditions of body temperature measurement. Body temperature was measured on the first day while the rats were under isoflurane anesthesia; on the second day, body temperature was measured while the rats were awake. Isoflurane has been reported to increase norepinephrine release in the preoptic area and induce hypothermia [31]. Since the body temperatures of the LPS and OLA groups on the second day were significantly higher than that in
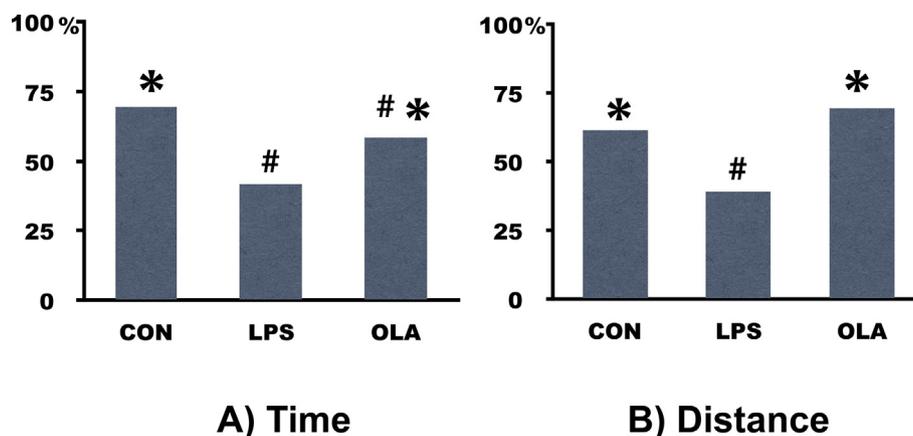
Figure 3. Percentages of successful trials in the Barnes maze test phase. A successful trial meant meeting the 10th training level outcomes (≤20 s time and ≤2.2 m distance). A) Time. B) Distance. Test trials were conducted three times in each rat. CON: control group, LPS: Surgery + lipopolysaccharide (LPS) group, OLA: Surgery + LPS + olanzapine group. *: vs. the LPS group (p < 0.05). #: vs. the CON group (p < 0.05).
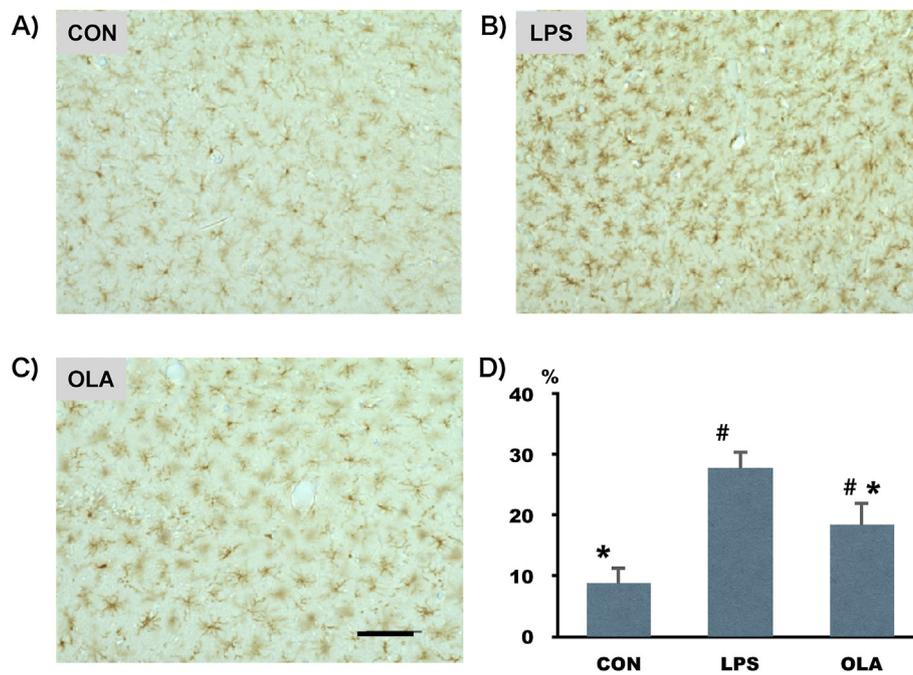
Figure 4. Typical Iba1 staining and staining area percentages in the hippocampus (cornu ammonis 2: CA2). A) CON: control group, B) LPS: Surgery + lipopoly-saccharide (LPS) group, C) OLA: Surgery + LPS + olanzapine group. D) Percentages of the Iba1 staining area in the hippocampus (CA2). Scale bar = 100 μm *: vs. the LPS group (p < 0.05). #: vs. the CON group (p < 0.05).

the CON group, we think that the administration of LPS and manipulation of the intestines induced pyrexia.

The microglial activity of the OLA group was lower than that of the LPS group, but there was no significant difference in plasma IL-1β concentration between these groups. Although TNF-α is reported to have a short half-life, with about a 95% reduced concentration at 3 h after surgery [32], high concentrations of TNF-α have been observed in the hippocampus of an aged rat POCD model, even at 7 days after surgery [19]. TNF-α concentrations might have been lower in the present study compared to the previous study because we used relatively young adult rats.

Microglial activity and IL-1β concentration did not change proportionally in the present study. The anti-POCD effects of olanzapine might not be dependent on the inhibition of plasma cytokines. Chronic administration of olanzapine has been reported to attenuate a potent neurotoxin-induced spatial memory impairment and hippocampal cell death in rats [33]. Upregulations of superoxide dismutase-1, pro- and

antiapoptotic proteins, and brain-derived neurotrophic factor have been suggested as possible mechanisms of olanzapine's protective effects. Olanzapine has also been reported to increase hippocampal pregnenolone and allopregnanolone after a single injection [34]. Pregnenolone and its sulfate have been reported to enhance learning and memory via N-methyl-D-aspartate receptors in a rodent model [35]. Allopregnanolone has been reported to decrease cell death and cognitive deficits after contusions to rats' prefrontal cortices [36]. Allopregnanolone has been speculated to reduce apoptosis and facilitate central nervous system repair in the contusion model. Furthermore, pain has been shown to be a risk factor of POCD in both animal and clinical studies [37, 38]. Acute stress has been reported to activate microglia in the hippocampus and other brain areas without changes in IL-1β levels [39]. Allopregnanolone might help to retain cognitive function via its analgesic and anxiolytic effects [40, 41]. George et al. [42] investigated the relationship of brain allopregnanolone levels and spatial long-term memory performance in young and aged rats and concluded that allopregnanolone might play a
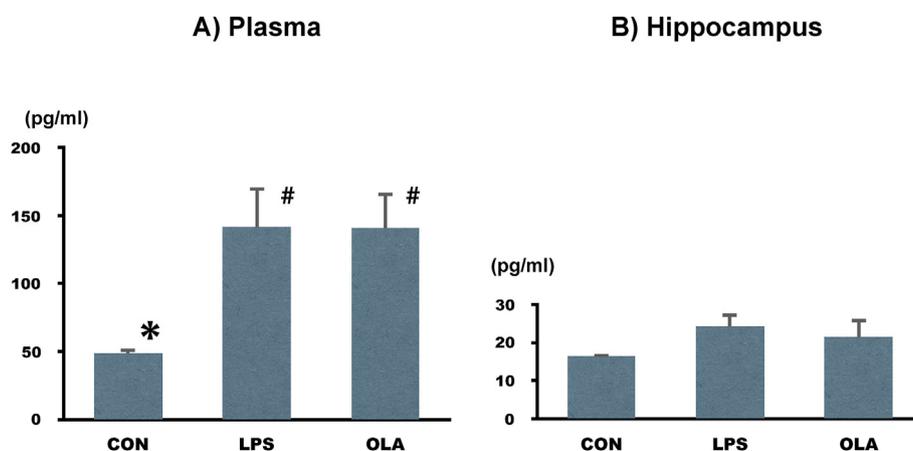
Figure 5. Plasma and hippocampal IL-1β concentrations. A) Plasma. B) Hippocampus. CON: control group, LPS: Surgery + lipopolysaccharide (LPS) group, OLA: Surgery + LPS + olanzapine group. *: vs. the LPS group (p < 0.05). #: vs. the CON group (p < 0.05).

critical role in age-related memory decline. In other words, the anti-POCD effects of olanzapine might depend on accelerated repair of and/or protection from secondary damage rather than inhibiting direct damage due to cytokines. Olanzapine might therefore become a candidate for POCD prevention.

There are several limitations to the present study. First, the dose dependency of olanzapine was not investigated because high-dose olanzapine induces sleepiness in rats. Second, although neuroinflammation is not the only possible mechanism of POCD, we did not investigate the other mechanisms, which include reduced hippocampal acetylcholine levels, mitochondrial dysfunction, oxidative stress, and blood-brain barrier damage [43, 44, 45]. Third, cytokine levels were measured only once, so a detailed analysis was not conducted. Further, since 6-month-old rats were used, the degree of POCD was mild. Since ovarian hormones have an antinociceptive effect and female rats are affected by reproductive cycle, we used male rats [46]. Results of the present study might be not applied to female rats. Although standard deviation of Iba1-staining area percentage in each section was small, animal number of control group in histopathological study was only two. Finally, in the histopathological evaluation and ELISA, we used larger LPS and olanzapine doses than in the Barnes maze test, as slight differences or changes in microglial activity and cytokine concentrations were predicted to be difficult to detect with smaller doses.

5. Conclusions

The effectiveness of olanzapine was investigated in an adult rat POCD model. Using Barnes maze tests a day after surgery, olanzapine was shown to attenuate spatial cognitive dysfunction; further, olanzapine inhibited microglial activity in the hippocampus 24 h after surgery. These effects of olanzapine were not related to IL-1β concentration in plasma and hippocampus. Olanzapine may therefore attenuate POCD via accelerated repair of and/or protection from secondary damage in the central nervous system.

Declarations

Author contribution statement

Keitaro Tachi: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Taeko Fukuda: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Makoto Tanaka: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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