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ORIGINAL ARTICLE

Propofol alleviates cisplatin-related cognitive impairment

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Abstract
Chemotherapy-related cognitive impairment (CRCI) is commonly reported following the administration of chemotherapeutic agents and comprises a wide variety of neurological problems. Many patients after chemotherapy need further surgery under anesthesia. Thus, in this study, we examined whether propofol, one of the most commonly used anesthetics in surgery, could further affect the cognitive abilities in mouse CRCI models. The mice were injected intraperitoneally with cisplatin (2 mg/kg/day) for continuous 10 days and showed significantly reduced body weights. After 10 days reconversion, mice with cisplatin injection showed impaired memory retention in the inhibitory avoidance (IA) task, mimicking the CRCI in patients. Then, we found that a single injection of propofol with the sub-anesthetic dosage (50 mg/kg) but not the anesthetic dosage (250 mg/kg) could significantly alleviate the cisplatin-induced memory impairment. These results imply the possible clinical application of propofol, especially at the sub-anesthetic dosage, in the surgery of patients after chemotherapy.

Keywords Propofol · Cisplatin · Chemotherapy-related cognitive impairment (CRCI)

Introduction

Recently, along with the development of technology of diagnosis and treatment of cancer, more and more patients are able to extend their life time. The improvement of their quality of life (QoL) has been becoming one of the most popular topics for clinical researchers [1]. Chemotherapy-related cognitive impairment (CRCI) is a cognitive dysfunction after chemotherapy, encompassing a broad range of neurological problems, such as impairments in memory, attention, executive functioning, and information processing speed [2, 3]. Furthermore, 13~70% tumor patients suffer different degree of CRCI [4–6] and up to 34% of patients experience persistent cognitive problems years after completing chemotherapy [7]. Cisplatin, one of the most commonly used neo-adjuvant chemotherapeutics, is the first widely used platinum anti-cancer agent in the treatment of several malignancies [8–10]; it can cross the blood-brain barrier and accumulates in the hippocampus [11, 12]. After treated with cisplatin, many patients consistently developed CRCI and impairment was detected in two or more cognitive domains in 40% of cisplatin chemotherapy recipients [13, 14]. It has been reported that continuous injection of cisplatin can also cause cognitive impairment in rodent models [15, 16].

As the method of the preoperative treatment of various malignant tumors, neo-adjuvant chemotherapy is widely accepted and becomes an important part of multidisciplinary treatment of various malignant tumors, and many patients after chemotherapy need further surgery under anesthesia. Propofol is one of the most commonly used anesthetics. In recent years, some studies have shown that propofol have dual effects on cognitive abilities through different mechanisms in both rodent models and patients [17–20]. However, little is known about the effects of propofol on CRCI. In this study, we examined the effects of propofol on the memory retention in a mouse CRCI model induced by cisplatin injection, and found that a single injection of propofol with the sub-anesthetic dosage (50 mg/kg) but not the anesthetic dosage (250 mg/kg) could significantly alleviate the cisplatin-induced memory impairment, suggesting a possible application of propofol in the surgery of patients after chemotherapy.

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Materials and methods

Animals

Animal care and experimental procedures were approved by Institutional Animal Care and Use Committee (Shanghai Institute of Planned Parenthood Research Animal Care). Adult female ICR mice (25–30 g) were obtained from SIPPR-B&K laboratory animal Corp (License Number: SCXK (Shanghai) 2013-0016). The mice were housed separately under standard laboratory conditions (12:12 light/dark cycle, 20~26 °C, 40~70% relative humidity) with free access to water and food. All mice were acclimated to the approved housing facility for 3 days before experiments. Mice were habituated for at least 2 h before behavioral tests, which were all performed between 1 p.m. and 5 p.m.

Drug treatments

Forty-eight adult female ICR mice weighing 25–35 g at the time of arrival served as subjects and were randomly divided into four groups: saline-treated controls (control, $n = 12$), cisplatin-treated (model, $n = 12$), cisplatin + propofol 50 mg/kg treated (Pro50, $n = 12$), and cisplatin + propofol 250 mg/kg treated (Pro250, $n = 12$). For cisplatin studies, mice were injected intraperitoneally (i.p.) with cisplatin (Sigma-Aldrich) dissolved in 0.9% saline (2 mg/kg/day) for 10 consecutive days ($n = 36$); then after 10 days reconversion, the avoirdupois of the mice was increasing, then the mice were tested with the inhibitory avoidance (IA) task described as follows: after the mice reached the 60s learning criterion, they immediately received propofol 50 mg/kg or 250 mg/kg intraperitoneally (i.p.) once. The control animals received 0.9% saline (i.p.) of the same volume ($n = 12$) (Schematic of the procedure used in this experiment can be seen in Fig. 1).

Inhibitory avoidance task

A continuous multiple-trial inhibitory avoidance (CMIA) paradigm was used for assessment of learning and memory as described elsewhere [21]. Briefly, for training, each animal was placed into the lit compartment of an IA apparatus (Tai meng technology co. LTD, Chengdu, China) facing away from the door (schematic diagram can be seen in Fig. 2). After 3 min, the door was lowered below the apparatus door to reveal the dark compartment. As the mouse stepped into the dark compartment with all four paws, a series of shocks (36 V) was delivered until the animal escaped back into the starting lit compartment. The door to the dark compartment remained open, and the mice could choose to either stay in the lit safe compartment or to re-enter the dark shock compartment. Mice that re-entered the shock compartment received another foot shock (36 V) and were allowed to escape immediately back into the lit compartment. Learning was considered to have occurred when mice avoided the shock compartment for ≥ 60 consecutive seconds. After the mice reached the 60s learning criterion, they immediately received drug administration as described above.

Memory retention was tested 24 h after the training session. No shocks were delivered during the memory testing trial. Each mouse was placed back into the starting light side of the apparatus with the door open, and the time taken (300 s as maximum) for each mouse to cross into the dark compartment was recorded.

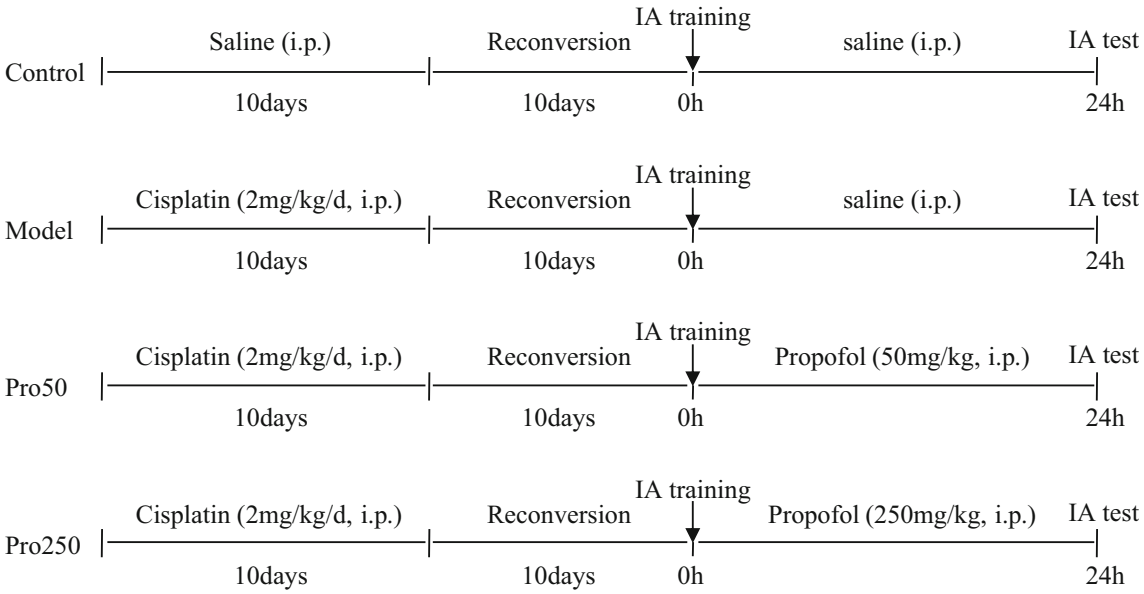

Fig. 1 Schematic of the procedure used in this experiment

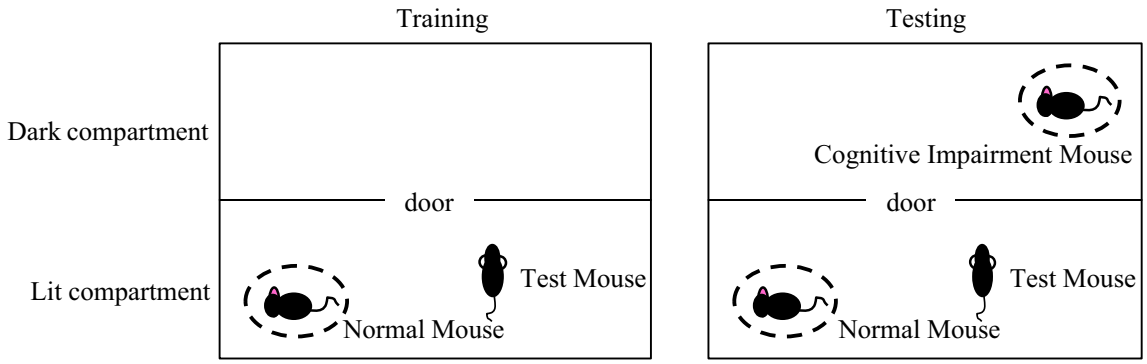

Fig. 2 Set up of the inhibitory avoidance task

Statistical analysis

Graphs and statistical analyses were prepared using GraphPad Prism 6.0 Software (GraphPad Software, La Jolla, CA, USA). Results were expressed as mean ± SEM. Comparison between groups were made by one-way ANOVA or two-way ANOVA. Statistical significance levels were set at 0.05.

Results

Cisplatin significantly decreases the body weights of mice

Mice were treated with daily i.p. injections of cisplatin (2 mg/kg) or 0.9% saline for continuous 10 days. The control group mice had normal behavior and body hair was smooth and shiny, and their body weights slightly increased daily (day 1: 26.31 ± 0.38 g, day 16: 27.88 ± 0.30 g; $n = 12$), while the cisplatin group mice showed a poor state and significantly reduced body weights (day 1: 26.31 ± 0.25 g, day 13: 17.88 ± 0.42 g, day 16: 20.44 ± 0.21 g; $n = 36$) (Fig. 3). From the injection day 3, the body weights of cisplatin group were significantly lower than those of the control group (Fig. 3),

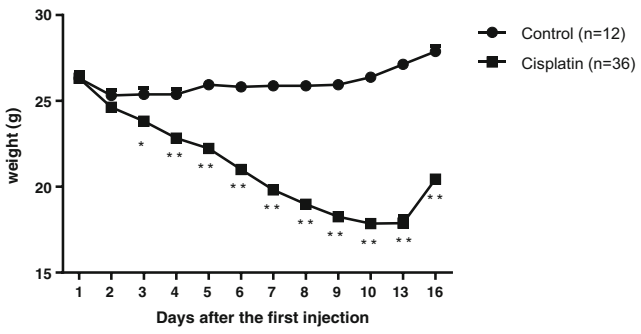

Fig. 3 The effect of cisplatin on the body weights of mice. Mice were treated with daily i.p. injections of cisplatin (2 mg/kg) or 0.9% saline for 10 days. All data are expressed as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$. $n = 12$ in the control group and $n = 36$ in the cisplatin group

indicating that cisplatin seriously affected the physical condition of mice.

The sub-anesthetic dosage (50 mg/kg) of propofol can alleviate the cisplatin-induced memory impairment

After 10 days reconversion, we examined the ability of memory retention by the inhibitory avoidance task. We randomly divided the cisplatin group ($n = 36$) into three groups: model, Pro50, and Pro250 ($n = 12$ for each group), which received a single injection of saline, propofol (50 mg/kg) and propofol (250 mg/kg), respectively. The memory retention latencies of the model group were significantly shorter as compared to the control group (model, 27.94 ± 4.12 s, $n = 12$; control, 289.47 ± 10.50s, $n = 12$; $P < 0.01$) (Fig. 4), suggesting the impaired memory retention induced by cisplatin injection. The sub-anesthetic dosage of propofol (50 mg/kg) could lengthen the memory retention latencies as compared to the model group (Pro50, 158.51 ± 31.22 s, $n = 12$; model, 27.94 ± 4.12 s, $n = 12$; $P < 0.05$) and partly rescued the cognitive impairment (Fig. 4). However, the anesthetic dosage of propofol (250 mg/kg) only slightly lengthened the memory retention latencies as compared to the model group without significant differences (Pro250, 86.01 ± 12.34 s, $n = 12$; model, 27.94 ± 4.12 s, $n = 12$; $P > 0.05$) (Fig. 4). These results showed that propofol at the sub-anesthetic dosage (50 mg/kg) had protective effect on the cisplatin-induced memory impairment in the mice.

Discussion

In this study, we developed a mouse model of cisplatin-induced cognitive impairment, and found that continuous injection of cisplatin significantly reduced the body weights of mice and impaired the memory retention in the IA task. It has been reported that cisplatin's neurotoxicity can affect the function of the central nervous system [22], and clinical studies have shown that cisplatin can impair the cognitive functions of

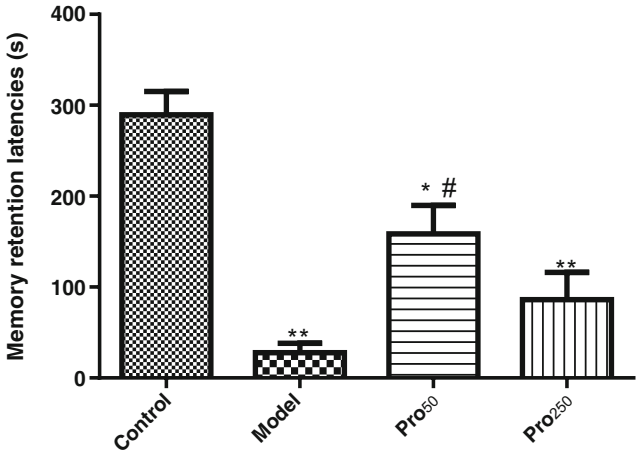

Fig. 4 The effects of propofol on mice's memory retention. After the mice reached the 60s learning criterion, they immediately received 0.9% saline (i.p.) (for control and model groups), propofol 50 mg/kg (Pro50) or 250 mg/kg (Pro250) intraperitoneally (i.p.) once. Memory retention was tested 24 h after the training session. The ability of memory retention is represented by the latency. All data are expressed as mean ± SEM. $n = 12$ for each group. (**$P < 0.01$ versus control, *$P < 0.05$ versus control, # $P < 0.05$ versus model)

patients [23]. Animal studies have also shown that cisplatin has negative effects on the exploratory behavior and memory length of rats [24]. Zhou and colleagues found that treatment of mice with cisplatin induces cognitive deficits that were associated with structural abnormalities in the brain [15]. Lomeli and colleagues found that mitochondrial dysfunction and increased oxidative stress were also involved in cisplatin-induced cognitive impairments [16].

Using this CRCI mice models, we found that the sub-anesthetic dosage (50 mg/kg, i.p.) but not the anesthetic dosage of propofol protected against the cisplatin-induced cognitive impairment. Hauer and colleagues have shown that propofol could enhance emotional memory consolidation in stressed rats by enhancing endocannabinoid signaling [20]. In animal models of neuronal injury, such as ischemic stroke and traumatic brain injury, propofol has also been reported to exert neuroprotective effects through suppression of inflammatory activity, reduction of oxidative stress and preventing the increase in neuronal mitochondrial swelling [25–27]. Emerging evidence suggests that cognitive impairment in patients with cancer is associated with persistent neuroinflammation [28–30]. Previous studies have shown that cisplatin-induced cognitive impairment is associated with reduced mitochondrial health in cerebral synaptosomes and mitochondrial abnormalities in the peripheral nervous system [15]. Thus, it is possible that propofol alleviated cisplatin-induced memory impairment through suppressing neuroinflammation, reducing oxidative and preventing the mitochondrial damage. The detailed mechanism still needs further study.

However, the higher anesthetic dosage of propofol (250 mg/kg) only slightly improves the memory retention abilities of the cisplatin-treated mice, and this effect was much lower than that of the sub-anesthetic dosage of propofol (50 mg/kg). It has been reported that the anesthetic dosage of propofol impaired learning and memory in rodent models and also caused retrograde amnesia in patients [31, 32]. Other research showed that propofol can cause dose-dependent neuroapoptosis [17]. Thus, this memory impairment and neuroapoptosis effects might weaken the neuroprotective effect of propofol with the dosage of 250 mg/kg.

In conclusion, using a cisplatin-induced mouse CRCI model, we found that a single injection of propofol with the sub-anesthetic dosage (50 mg/kg) but not the anesthetic dosage (250 mg/kg) could significantly alleviate the cisplatin-induced memory impairment. These findings are clinically relevant because of increasing evidence that patients treated for cancer with platinum-based compounds frequently develop cognitive impairment and structural abnormalities in the brain. Our current results imply the potential application of propofol in the surgery of patients after chemotherapy and urge for a clinical trial on the potential beneficial effects of propofol on the cognitive functions of patients treated with cisplatin.

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Compliance with ethical standards Animal care and experimental procedures were approved by Institutional Animal Care and Use Committee (Shanghai Institute of Planned Parenthood Research Animal Care).

Conflict of interest The authors declare that they have no conflict of interest.

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