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Glucose prevents cisplatin-induced fatigue-like behavior in mice

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ABSTRACT

Fatigue is recognized as one of the most common and distressing side effects of cancer and anticancer therapy. In the present study, we used mice without cancer to examine the specific influence of chemotherapy on fatigue. Mice were administered a single dose of cisplatin (CDDP; 10 mg/kg, i.p.) or saline as a control, and then were treated with glucose (500 or 5000 mg/kg p.o.), olive oil (10 ml/kg p.o.), or saline daily for 4 days. At 24 h after the final dose of glucose, olive oil, or saline, fatigue-like behavior was investigated by assessment of running activity on a treadmill. After administration of CDDP, running activity of mice decreased significantly. In addition, mice treated with CDDP showed significant weight loss compared with control mice. In CDDP-treated mice, daily administration of glucose caused a significant and dose-dependent increase of both the liver glycogen content and running activity. Although blood glucose levels were higher in the CDDP + olive oil group than in the CDDP + saline group, daily administration of olive oil did not increase either liver glycogen or running activity. These results suggest that maintenance of the liver glycogen content prevented fatigue-like behavior in mice after administration of CDDP.

1. Introduction

Fatigue is considered to be among the most frequent and undesirable adverse effects of cancer and treatment for cancer. The National Comprehensive Cancer Network defined cancer-related fatigue as an unusual and persistent sensation of tiredness related to cancer or cancer therapy that interferes with usual functioning. Cancer-related fatigue is thought to affect more than 70% of cancer patients, with some reports indicating that the prevalence is as high as 80%–99% for patients currently undergoing treatment [1]. This fatigue can have a dramatic effect on the quality of life, capacity for self-care, and willingness to continue treatment, thus influencing overall survival [1]. Despite the very high prevalence of fatigue, there has been little research on the underlying mechanisms. Perhaps this is not surprising given the complexity of the phenomenon, since both cancer itself and treatments like chemotherapy cause fatigue, with the relative contribution of each being unclear.

In clinical studies, fatigue is typically measured by self-reported assessment or quantitative scales [2], whereas the level of fatigue must be inferred from behavior in animal studies. Several methods have been established for assessing voluntary activity in rodents, including wheel running, home cage activity, burrowing, and open field activity [3–5]. Some authors have already examined the independent effect of chemotherapy on fatigue in rodent models without cancer [6–9].

During prolonged exercise at moderate to high intensity, carbohydrates are primarily utilized to support energy metabolism due to their efficiency and ready availability as an energy source [10,11]. In humans, the majority of endogenous carbohydrate is stored as glycogen in the muscles and liver, and the capacity to sustain muscle contraction during moderate to high intensity exercise is highly dependent on the available glycogen stores [12]. The relevant physiological mechanisms appear to include several interrelated factors, such as maintenance of normoglycemia and attenuation of central nervous system fatigue, glycogen sparing, and reduction of exercise-induced strain [13].

Cisplatin (CDDP) is one of the most effective anticancer agents, and it is widely used in the treatment of various malignancies, including leukemia and cancer of the head & neck, lung, ovary, breast, brain, kidney, and testicle [14]. However, treatment with CDDP is often stopped due to impairment of the quality of life by anorexia associated with nausea and vomiting. Anorexia causes malnutrition and decreases energy stores. We hypothesized that CDDP-induced anorexia would be associated with fatigue and that glucose might improve CDDP-induced fatigue-like behavior.

Accordingly, this study was performed to examine the effects of chemotherapy on fatigue in mice by measuring the impact on treadmill exercise, and to assess whether depletion of liver glycogen influenced fatigue. Because both cancer itself and treatment for cancer are known to cause fatigue, we examined healthy mice to identify the specific

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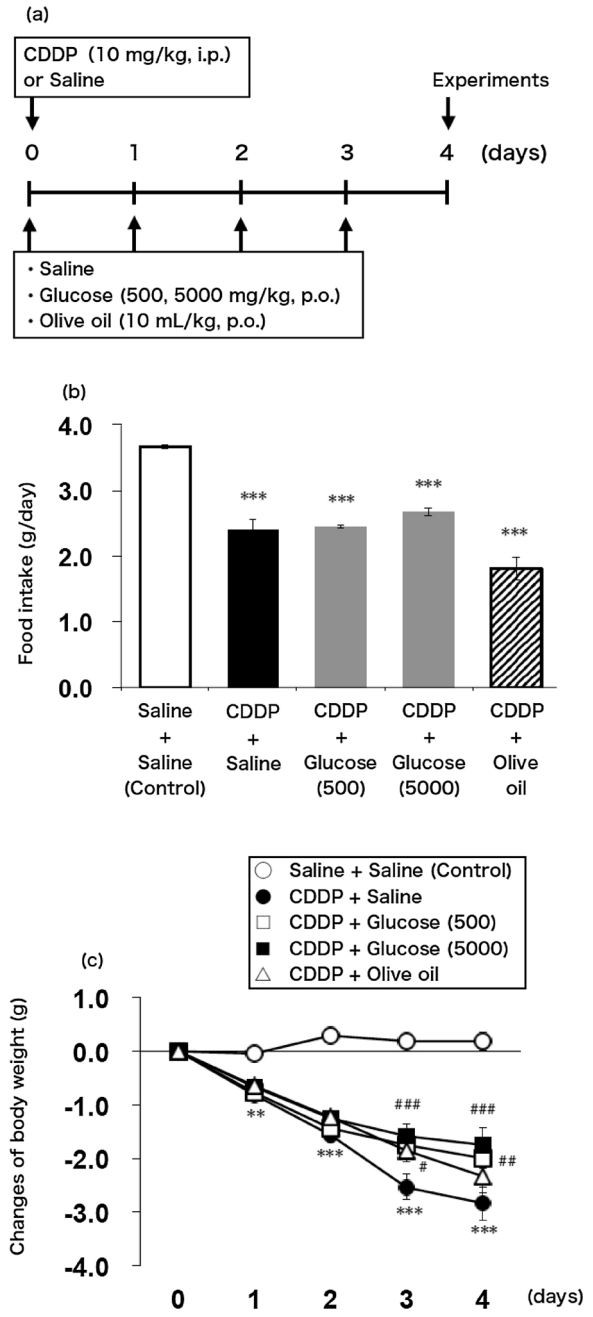

Fig. 1. CDDP reduces food intake and body weight in mice.
(a) Experimental protocol. CDDP (10 mg/kg) was administered to all mice on Day 0, except for control mice. Then glucose (500 or 5000 mg/kg), olive oil, or saline was administered from Day 0 to Day 3. (b) CDDP-treated mice showed lower food intake compared with the control group. Data are presented as the mean ± SEM (n = 8). Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test. ***$p < 0.005$ versus the control group. (c, d) CDDP-treated mice showed a lower body weight compared with the control group. Data are presented as the mean ± SEM (n = 8). Statistical analyses were performed with two-way ANOVA followed by the Bonferroni multiple comparisons test. **$p < 0.01$, and ***$p < 0.005$ versus the control group; #$p < 0.05$, ##$p < 0.01$, and ###$p < 0.005$ versus the CDDP + saline group.

influence of chemotherapy

2. Materials and methods

2.1. Animals

Male C57BL/6 J mice (7 weeks old at the time of the experiments) were purchased from Japan SLC (Shizuoka, Japan). The animals were housed in groups of four per cage, and food and water were provided *ad libitum*. The room temperature was controlled at 23 °C ± 1 °C, and a 12 h light-dark cycle was maintained (lights on 8:00 to 20:00 h). The experimental protocols were approved by the Institutional Animal Care and Use Committee of Tokyo University of Science, and studies were conducted according to the guidelines of the National Institute of Health and the Japan Neuroscience Society.

2.2. Treatment

Mice were administered a single dose of CDDP (10 mg/kg, i.p.) or saline as a control. Then the mice were given saline, glucose (500 or 5000 mg/kg p.o.), or olive oil (10 ml/kg p.o.) once daily for 4 days (Fig. 1a). Body weight and food intake were recorded daily for 5 days.

2.3. Treadmill fatigue test

At 24 h after the final dose of saline, glucose, or olive oil, fatigue-like behavior was assessed in the mice by using treadmill exercise as an index of whole-body exercise capacity, as described previously (Dougherty et al., 2016). During the treadmill test, each mouse was forced to run on a motor-driven treadmill (TMS-2; Melquest, Toyama, Japan). About one week before the test, the mice were subjected to the same treadmill protocol (Table 1), and only animals that ran more than 460 m (26 m/min × 5 min) were selected for use in the present study.

First, a 10 min warm-up period was provided with the treadmill set at 10–15 m/min and 0° inclination. After warm-up, the treadmill inclination was fixed at 10°. The test was started at a speed of 20 m/min, and the speed was increased by 2 m/min every 5 min until the mouse reached exhaustion. Exhaustion was defined as spending 10 s on the shocker plate without attempting to re-engage the treadmill. The workload was calculated as the product of the running distance until exhaustion and the body weight.

2.4. Measurements of blood glucose and ketone levels

Different animals from those for the treadmill fatigue test were used in this experiment. At 24 h after the final dose of saline, glucose, or olive oil, blood glucose and ketone (β-hydroxybutyrate) levels in 2 h fasted mice were measured in a blood sample from the tail vein by using a Precision Xceed blood glucose and ketone monitoring system (Abbott Japan Co., Ltd., Chiba, Japan).

Table 1
Treadmill fatigue test protocol.

	Inclination	Speed (m/min) × Time (min)
Warm-up period	0°	10 m/min × 5 min
		15 m/min × 5 min
Test period	10°	20 m/min × 5 min
		22 m/min × 5 min
		24 m/min × 5 min
		26 m/min × 5 min
		28 m/min × 5 min
		30 m/min × 5 min
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2.5. Measurement of the liver glycogen content

Different animals from those for the treadmill fatigue test were used in this experiment. At 24 h after the final dose of saline, glucose, or olive oil, the non-fasted mice were killed under deep isoflurane anesthesia, their livers were removed, and the wet weight was measured. Then 600 mg of liver tissue was ground for extraction. For hydrolysis of glycogen, 1.0 ml of the extract was heated with 1.2 ml of concentrated HCl for 2 h at 100 °C. After neutralization of the HCl with alkali and adjustment of the volume to 2.5 ml with water, the measurement of the resulting glucose solution was done using a glucose sensor (Precision Xceed; Abbott Japan Co., Ltd.).

2.6. Measurements of skeletal muscles and adipose mass

Different animals from those for the treadmill fatigue test were used in this experiment. At 24 h after the final dose of saline, glucose, or olive oil, the non-fasted mice were killed under deep anesthesia with isoflurane, their gastrocnemius and tibialis anterior muscles, which mainly comprise fast muscle fibers, the soleus muscle, which mainly comprises slow twitch fibers, and epididymal adipose tissues were removed and their wet weights measured.

2.7. Drugs

The drugs used in the present study were purchased from the following manufacturers: cisplatin solution was obtained from Pfizer, Co., Ltd. (Tokyo, Japan), glucose solution was from Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan), and olive oil was from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

2.8. Statistical analysis

Results are expressed as the mean ± standard error of the mean (SEM). Differences were evaluated by one-way analysis of variance (ANOVA) or two-way ANOVA, followed by the Bonferroni multiple comparisons test. All statistical analyses were performed with Prism version 5.0 (GraphPad Software, CA, USA).

3. Results

3.1. Food intake and body weight

CDDP administration led to a significant decrease of food intake (Fig. 1b; ***p < 0.005 vs. control group) and body weight (Table 2, Fig. 1c; ***p < 0.005 vs. control group), with these changes not being prevented by administration of olive oil (Table 2, Fig. 1b, c). Although daily administration of glucose did not affect food intake (Fig. 1b), there was a slight prevent body weight loss compared with the CDDP + saline group (Fig. 1c; #p < 0.05, ##p < 0.01, and ###p < 0.005 vs. CDDP + saline).

Table 2
Body weight (g).

Group	Day 0	Day 1	Day 2	Day 3	Day 4
Saline + saline (control)	21.15 ± 0.18	21.10 ± 0.18	21.45 ± 0.15	21.34 ± 0.22	21.34 ± 0.23
CDDP + saline	22.46 ± 0.57	21.65 ± 0.59	20.89 ± 0.52	19.93 ± 0.34	19.61 ± 0.33
CDDP + glucose (500 mg/kg)	22.10 ± 0.46	21.34 ± 0.44	20.65 ± 0.43	20.34 ± 0.43	20.10 ± 0.47
CDDP + glucose (5000 mg/kg)	23.13 ± 0.23	22.45 ± 0.23	21.86 ± 0.19	21.54 ± 0.12	21.38 ± 0.17
CDDP + olive oil	22.34 ± 0.45	21.69 ± 0.43	21.10 ± 0.41	20.49 ± 0.55	20.00 ± 0.61

N = 8; mean ± SEM.

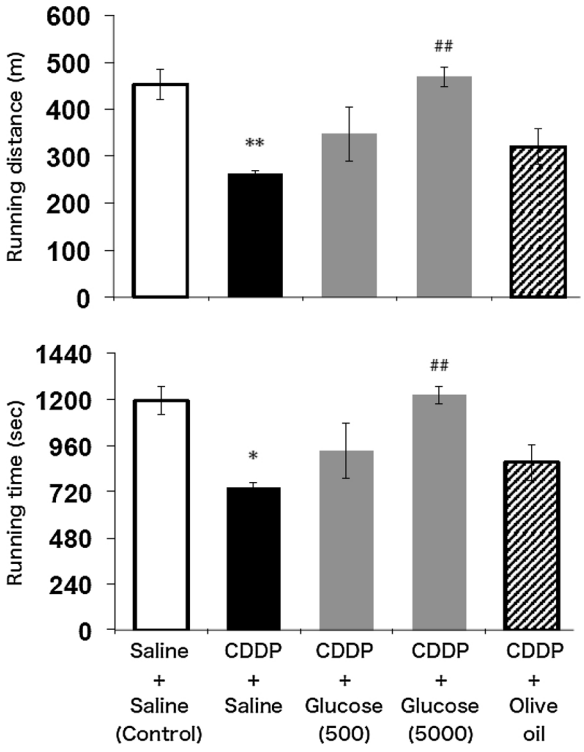

Fig. 2. CDDP induces fatigue-like behavior in mice.
On Day 0, mice received administration of CDDP (10 mg/kg) or saline. On Day 4, mice underwent the treadmill fatigue test. Each column represents the mean ± SEM for 6 mice. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test. *p < 0.05, and **p < 0.01 versus the control group; ##p < 0.01 versus the CDDP + saline group.

3.2. Treadmill fatigue test

The workload, the distance run, and the running time to exhaustion in the treadmill test were all significantly reduced in the CDDP + saline group compared with the control group (Fig. 2; *p < 0.05, **p < 0.01 vs. control). On the other hand, these reductions showed significant dose-dependent improvement in the CDDP + glucose group (Fig. 2; ##p < 0.01 vs. CDDP + saline). However, there was no improvement in the CDDP + olive oil group compared with the CDDP + saline group.

3.3. Blood glucose and ketone levels

The blood glucose level was lower in the CDDP + saline group and CDDP + glucose group than in the control group on Day 4, while blood ketone levels were similar among the 3 groups (Table 3).

Table 3
Blood glucose and ketone levels (n = 6; mean ± SEM).

Group	Blood glucose (mg/dl) in 2 h fasting state	Blood β-OHB (mmol/l) in 2 h fasting state
Saline + saline (control)	208 ± 2.9	0.58 ± 0.07
CDDP + saline	163 ± 8.6	0.82 ± 0.07
CDDP + glucose (500 mg/kg)	168 ± 5.0	0.63 ± 0.02
CDDP + glucose (5000 mg/kg)	163 ± 9.6	0.85 ± 0.11
CDDP + olive oil	185 ± 6.9	0.90 ± 0.08

β − OHB = β-hydroxybutyrate.

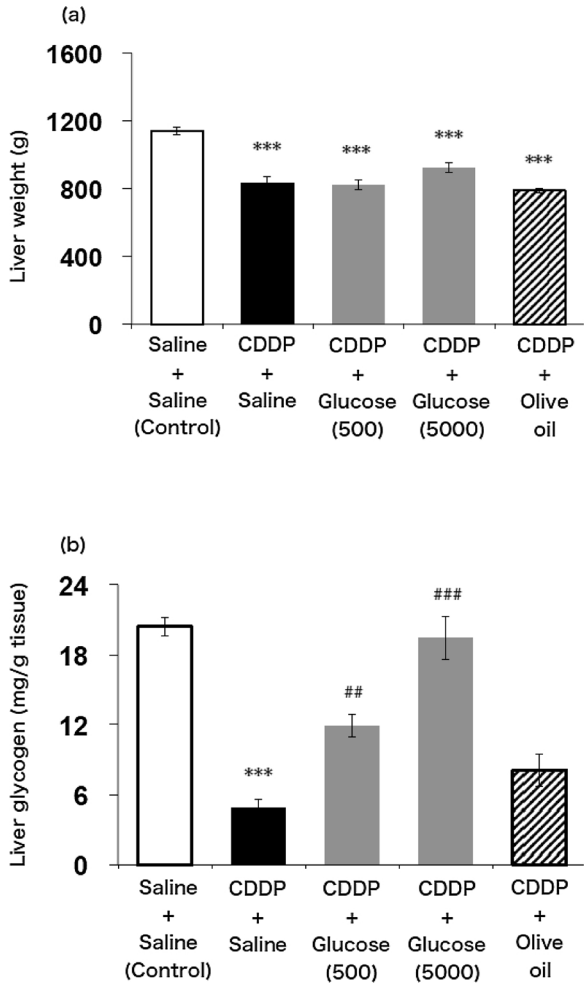

Fig. 3. Liver weight and liver glycogen content in CDDP-treated mice.
On Day 4, the liver weight was measured (a) and the liver glycogen content was determined (b). Each column represents the mean ± SEM for 6 mice. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test. ***$p < 0.005$ versus the control group; ##$p < 0.01$, and ###$p < 0.005$ versus the CDDP + saline group.

3.4. Liver weight and liver glycogen content

We examined the changes of liver weight and the liver glycogen content following administration of CDDP. In all CDDP-treated groups, liver weight showed a significant decrease compared with that in the control group (Fig. 3a; ***$p < 0.005$ vs. control), while liver weight was similar among the CDDP-treated groups (Fig. 3a). In the control group, the liver glycogen content was 20.4 ± 0.8 mg/g tissue (Fig. 3b). In contrast, the liver glycogen content was decreased to 4.9 ± 0.7 mg/g tissue in the CDDP + saline group, being approximately one quarter of that in the control group (Fig. 3b; ***$p < 0.005$ vs. control). In the CDDP + glucose (5000 mg/kg) group, the liver glycogen content was 19.4 ± 1.9 mg/g tissue, being similar to that in the control group (Fig. 3b; ##$p < 0.01$, ###$p < 0.005$ vs. CDDP + saline). In the CDDP + olive oil group, the liver glycogen content was 8.1 ± 1.4 mg/g tissue and was low like that in the CDDP + saline group (Fig. 3b).

3.5. Skeletal muscles and adipose mass

CDDP administration significantly decreased weight of the skeletal muscles (Fig. 4a–c; **$p < 0.01$, and ***$p < 0.005$ vs control group). These decreases were prevented by the CDDP + glucose groups (Fig. 4a–c; #$p < 0.05$, and ###$p < 0.005$ vs. CDDP + saline group). Similarly, adipose mass decreased significantly after administration of CDDP, and the decreases were prevented by the CDDP + glucose groups (Fig. 4d; ***$p < 0.005$ vs. control group, ###$p < 0.005$ vs. CDDP + saline group).

4. Discussion

Fatigue is one of the most common side effects of anticancer therapy; it not only impairs the quality of life, but also diminishes physical activity, limits treatment, and increases morbidity [15]. Deugherty et al. [9] reported the use of a treadmill test to measure fatigue-like behavior in mice. Their method has several advantages over voluntary wheel running activity, a common preclinical assay of fatigue-like behavior. Voluntary wheel running requires mice to electively interact with the test apparatus. However, some inbred strains of mice rarely interact with the wheel [16] and perform so little running activity that it may be difficult or impossible to identify a fatigue-induced decrease of activity. In contrast, the treadmill fatigue test eliminates free choice and provides a useful method of assessing fatigue-like behavior for mice that do not run on wheels. Accordingly, we examined the influence of CDDP on fatigue in mice by using this treadmill test. Several methods have been established for assessing voluntary activity in rodents [6–9]. However, previous studies have suggested that wheel running may be more sensitive than is home-cage activity in detecting chemotherapy-related fatigue [6]. We chose treadmill assessment and did not examine wheel running or home cage activity, further research is needed to elucidate these relationships.

Administration of CDDP to mice led to a significant decrease of running activity, and mice treated with CDDP showed significant weight loss compared to control mice. The observed weight loss was due to anorexia. Weight loss is an indicator of general health and a decrease of weight may contribute to fatigue [17]. In the present study, daily administration of glucose led to slight prevent body weight loss and improved running activity compared with the CDDP + saline group. Similarly, we found that daily intake of a carbohydrate-enriched oral nutritional supplements increased the running activity of CDDP-treated mice compared with daily intake of a fat-enriched oral nutritional supplements (unpublished data). It has been reported that mice fed a high-fat diet or a high-carbohydrate diet show weight gain compared with mice on a standard diet [18]. In addition, mice fed a high-fat diet show more weight gain than mice fed a high-carbohydrate diet, probably due to higher caloric intake with the high-fat diet. However, daily administration of olive oil failed to prevent CDDP-induced body weight loss in the present study. Therefore, gain weight seems to be easier with intake of glucose (carbohydrate) than with intake of olive oil (fat) in mice that have CDDP-induced anorexia. In addition, CDDP administration significantly decreased muscle and fat mass compared with control group. Glucose prevented CDDP-associated loss of muscle and fat mass. Taken together, these results suggest that preventing weight loss due to daily intake of glucose at least partly contributed to an increase of running activity.

It is well known that hypoglycemia suppresses brain function during exercise, and this often leads to inability to continue exertion [19], while blood glucose homeostasis plays an important role in prolonging endurance exercise [20]. Liver glycogen is an important source of blood glucose for readily available energy. During exercise, energy sources such as glucose and liver glycogen stores become depleted, leading to fatigue [20]. Depletion of liver glycogen might be an important factor in the development of fatigue during exercise because lack of glycogen results in inability to maintain the blood glucose level, and ensuing hypoglycemia can lead to impairment of nervous function [20]. In the present study, daily administration of glucose to mice led to a significant and dose-dependent increase of both the liver glycogen content and running activity. Although the blood glucose level was higher in the CDDP + olive oil group than in the CDDP + saline group, daily administration of olive oil failed to increase the liver glycogen content

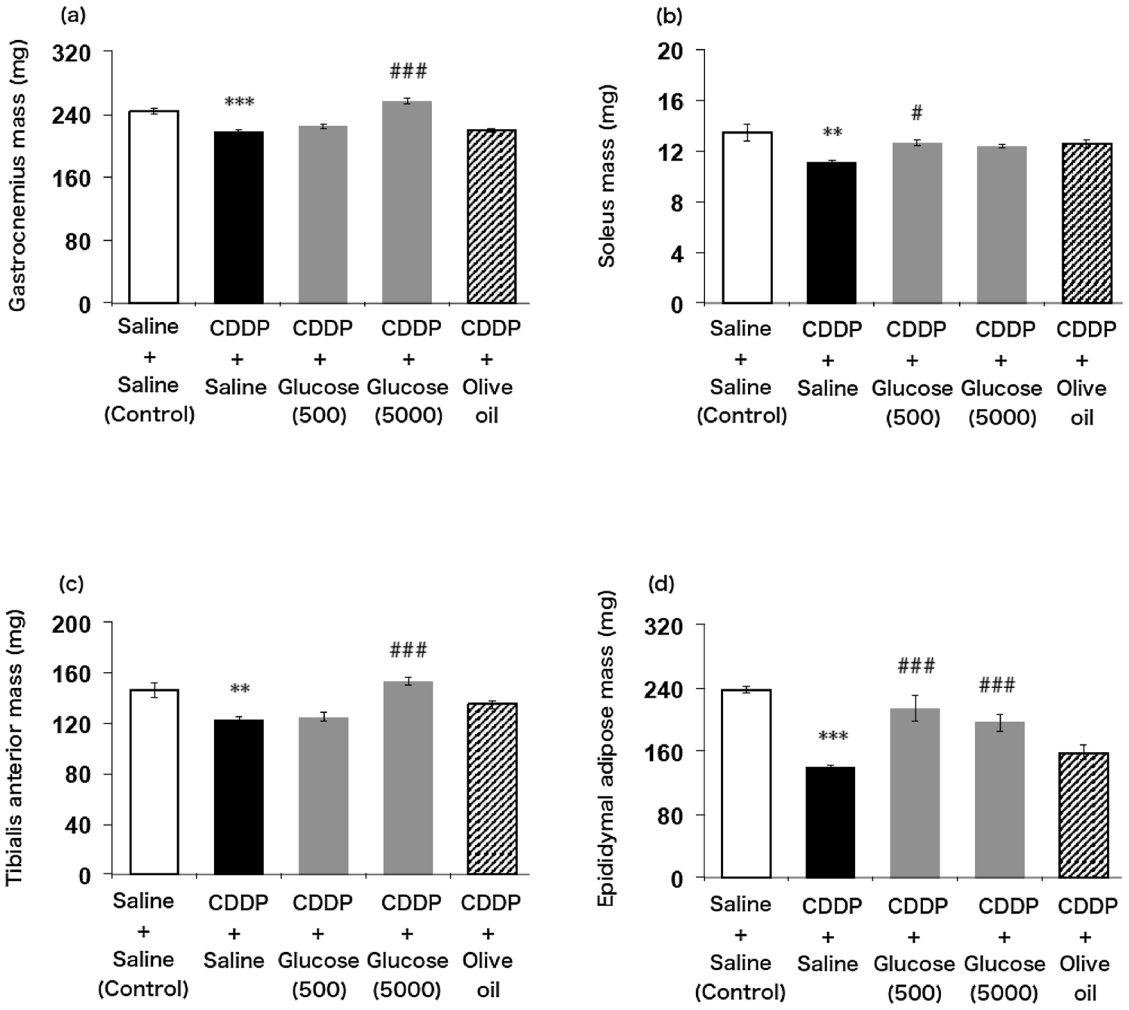

Fig. 4. Skeletal muscles and adipose mass in CDDP-treated mice.
On Day 4, the gastrocnemius (a), tibialis anterior (b), soleus (c), and epididymal adipose (d) weight were measured. Each column represents the mean ± SEM for 6 mice. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test. $^{**}p < 0.01$, and $^{***}p < 0.005$ versus the control group; $\#p < 0.05$, and $\#\#\#p < 0.005$ versus the CDDP + saline group.

and running activity. These results indicate that preservation of liver glycogen stores prevented fatigue-like behavior after CDDP administration. Furthermore, CDDP-induced anorexia may affect blood glucose homeostasis and depletion of liver glycogen. Although the mechanism is unknown, administration of glucose may contribute to the maintenance of liver glycogen rather than the blood glucose level. In the present study, glycogen levels were measured in the liver, but not skeletal muscles, of the CDDP treated mice. Previous studies have shown that the muscle glycogen levels of fasted mice were significantly decreased, compared with the fed mice [21]. In addition, 5-fluorouracil treated mice significantly decreased the running wheel activity and forced swimming time compared with the normal mice [22]. Consistent with the behavioral data, the level of glycogen in the 5-fluorouracil treated group was significantly decreased, compared with the normal group [22].

CDDP treatment has been associated with several toxic side effects including nephrotoxicity, hepatotoxicity, and neuropathy [14]. In laboratory animals, renal toxicity (increase in BUN), gastrointestinal toxicity (incidence of diarrhea), and bone marrow toxicity (decrease in total leukocytes) were observed with respect to the doses ranging from 25 to 45 μmol/kg (approximately 8–14 mg/kg) of CDDP administration [23]. However, hepatotoxicity was not apparent at similar doses (approximately 6–15 mg/kg) of CDDP-treated mice [24]. In addition, mechanical allodynia and hyperalgesia were not observed after CDDP was administered intraperitoneally at a dose of 10 mg/kg (unpublished data). Therefore, while renal toxicity and bone marrow toxicity may be playing a role in fatigue-like behavior, further research is needed to fully elucidate these relationships.

Warburg et al. [25] found that most cancer cells rely more heavily on glycolysis than oxidative phosphorylation to produce energy compared with normal cells, even under normoxic conditions. Thus, cancer cells are more dependent on glucose than normal cells, and it has been reported that both murine and human carcinomas grew more slowly in mice on a low carbohydrate and high protein diet compared with a mice on a Western diet characterized by relatively high carbohydrate and low protein intake [26]. In addition, Poff et al. [27] reported that the ketogenic diet (a low carbohydrate and high fat diet) significantly increased the mean survival time of mice with metastatic cancer. It is important to note that animals fed the ketogenic diet lost approximately 10% of their body weight during the study [27]. While a low carbohydrate diet has been shown to slow cancer progression, it would be unlikely to prevent cancer-related fatigue-like behavior. Because we examined mice without cancer to determine the specific effect of chemotherapy on fatigue, we did not evaluate whether administration of glucose could influence tumor growth. This is a limitation of the present study.

In conclusion, glucose prevented CDDP-induced fatigue-like behavior in mice, while a preventive effect was not observed in mice given

olive oil. Glucose may improve the quality of life during treatment with anticancer agents by preventing fatigue.

Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

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