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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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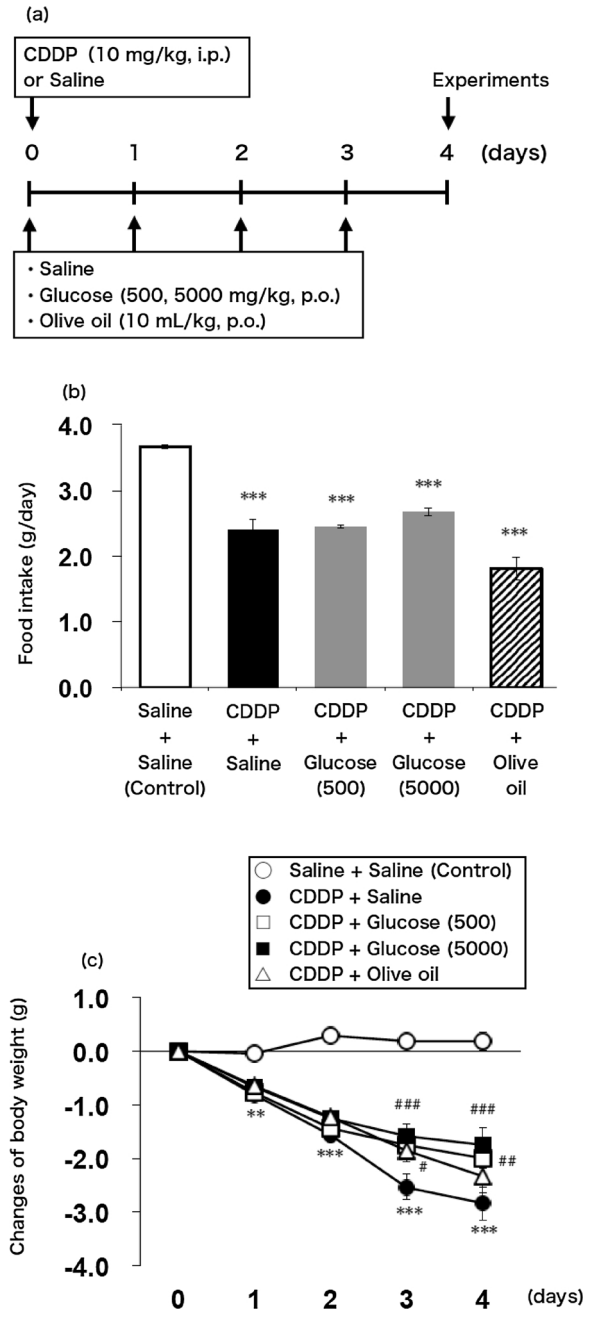

Fig. 1. CDDP reduces food intake and body weight in mice.
(a) Experimental protocol. CDDP (10 mg/kg) was administered to all mice on Day 0, except for control mice. Then glucose (500 or 5000 mg/kg), olive oil, or saline was administered from Day 0 to Day 3. (b) CDDP-treated mice showed lower food intake 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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