主論文の要旨

D-Allulose Improves Endurance and Recovery from Exhaustion in Male C57BL/6J Mice

（D-アルロースは雄性C57BL/6Jマウスの持久力と運動疲労よりの回復を改善する）

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【Introduction】

D-Allulose is a rare, functional sugar formed by the epimerization of D-fructose at the C-3 position, which has been shown to ameliorate insulin resistance and glucose tolerance in rodents and humans and reduce abdominal fat accumulation in rodents and humans. It has been reported that daily intake of D-allulose may accelerate the repletion of liver and muscle glycogen after exhaustive swimming. Long-term administration of a rare sugar syrup containing D-allulose enhanced the translocation of liver glucokinase and increased liver glycogen content. In addition, others showed that D-allulose promoted fat oxidation, and enhancement of postprandial fat oxidation in response to D-allulose intake has also been reported in healthy humans.

We hypothesized that D-allulose would enhance exercise performance because its administration has been shown to increase muscle or liver glycogen storage and fat oxidation. In the present study, we assessed whether D-allulose administration improves endurance ability and accelerates recovery from exhaustion. We further compared the effects of D-allulose with exercise training effects to understand its mechanism of action.

【Materials and Methods】

Six-week-old male C57BL/6J mice were singly housed in cages and allowed free access to a standard chow diet (MF powders) and water from the period of environmental adaptation until the beginning of the experiment. During the intervention period, mice were either kept on the chow diet (AIN93G powder, including 3% cellulose) or a D-allulose diet (AIN93G powder, including 3% D-allulose). To standardize the number of calories in the diets, D-allulose was replaced with cellulose. A free-wheel running apparatus was placed into individual cages housing mice assigned to exercise, and the mice were allowed to run freely on the wheels. Food intake was measured once every 2 days. Body weights were measured weekly.

1. Experiment 1: Effect of Long-Term D-Allulose Administration on Aerobic Performance (Figure 1)

Mice were randomly assigned into two groups: a chow diet group (E1 group, $n = 6$) and a D-allulose diet group (AE1 group, $n = 7$). Running wheels were placed in all cages. All mice performed the first endurance and recovery tests on a chow diet. The second endurance and recovery tests were performed after 4 weeks of administration of either a chow diet or a D-allulose diet.

2. Experiment 2: Effect of Long-Term D-Allulose Administration on Maximal Aerobic Speed and Physiological Indicators Related to Aerobic Performance (Figure 2)

Ten-week-old mice were divided into four groups: sedentary/chow diet group (C2, $n = 6$), sedentary/D-allulose group (A2, $n = 6$), exercise/chow diet group (E2, $n = 6$), and exercise/D-allulose group (AE2, $n = 7$). Mice in the exercise groups (E2 and AE2) had free

access to the wheel after the grouping at the start of Week 3. The first MAS and BGL tests were performed before the grouping. The second tests and ipGTT were conducted 4 weeks after the grouping. Mice were euthanized by cervical dislocation immediately after running on the treadmill at 20 m/min for 30 min at the end of Week 8. Muscles and liver were immediately removed and subsequently frozen in liquid nitrogen for further analysis (liver and muscle glycogen levels, western blots).

3. Experiment 3: Effect of Short-Term D-Allulose Administration on MAS, Blood Glucose, and Blood Lactate Levels (Figure 3)

Mice (n = 6) were on an alternate feeding regimen of chow diet or D-allulose. We measured both glucose and lactate levels before and after each MAS test.

【Results】

1. Experiment 1

D-Allulose Improves Endurance and Recovery. (Figure 4).

2. Experiment 2

D-Allulose administration increased the maximal aerobic speed (MAS)(Figure 5). D-Allulose also suppressed blood lactate increase after 2 hours running (Figure 6). Although D-allulose did not change the overall glucose levels as determined by ipGTT, it decreased plasma insulin levels, indicating enhanced insulin sensitivity (Figure 7). D-Allulose and exercise intervention did not significantly affect liver and muscle weight in mice, but significantly reduced white fat weight, and the combination of the two further enhanced this effect (Table 1). D-Allulose increased liver glycogen but not muscle glycogen levels (Figure 8). Finally, D-allulose enhanced the phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) and the expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) (Figure 9).

3. Experiment 3

D-Allulose administration increased the MAS and suppressed blood lactate increase after the MAS test, which was even observed following treatment for >3 or 7 days (Figure 10).

【Discussion】

The effects of D-allulose on aerobic exercise performance can depend on the availability of carbohydrates and fat, which are the main sources for ATP production. Glycogen contents in the muscles and liver are associated with endurance and recovery from exhaustive exercise. In our study, both the voluntary running distance and the MAS increased after short-term administration of D-allulose. These effects of D-allulose may be due to increased levels of liver glycogen. However, D-allulose can also impact exercise performance through changes in fat oxidation.

Lipids are another primary source for the production of ATP. During muscle contraction,

the uptake of fatty acids in skeletal muscle increases, while the activity of ACC decreases, which promotes the phosphorylation of ACC. PGC-1α is involved in the regulation of energy metabolism and mitochondrial biogenesis. Long-term aerobic exercise training significantly affects the AMPK-PGC-1α pathway. We found that D-allulose administration enhanced the AMPK axis, which is consistent with D-allulose enhancing the oxidation of fatty acids. A strong fat-oxidation ability increases the endurance exercise capacity.

The accumulation of blood lactate indicates the aerobic/anaerobic transition and is an important marker for endurance exercise capacity. In the present study, blood lactate levels after 2 h of endurance running at moderate intensity were lower after 4 weeks of D-allulose administration or exercise training. As the intensity of endurance running was likely to be below the lactate threshold levels, the difference in lactate levels is possibly because of the improved utilization of fatty acid rather than the increased synthesis of lactate. In the MAS test, even short-term administration (e.g., 3 days) of D-allulose effectively reduced lactate levels after running. As lactate levels are expected to increase if increased liver glycogen is driving the improvement in MAS, we speculate that the improvement in MAS can be, at least in part, because of improved fat oxidation. Blood glucose levels significantly decreased during the period of chow diet administration but not during the D-allulose administration period, which suggests that D-allulose administration increased glycogen levels or the preferred use of free fatty acid.

【Conclusion】

The present data indicated that D-allulose can prevent fatigue during or after exercise. Our study not only provides valuable insights into the potential role of D-allulose in alleviating obesity and enhancing aerobic exercise performance in humans but also conclusively establishes a viable and promising option to ameliorate the clinical outcomes of obesity-induced health problems by using D-allulose.