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Time-restricted feeding on weekdays restricts weight gain: A study using rat models of high-fat diet-induced obesity

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HIGHLIGHTS

- A time-restricted feeding regimen (TRF) was tested, i.e., no food consumption during inactive phase daily for 5 weekdays, but not for weekend.
- This special TRF restricted weight gain in juvenile rats.
- Total calorie intake per week was not reduced by this special TRF regimen.

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ABSTRACT

A recent study reported that a special weekly scheduled time-restricted feeding regimen (TRF), i.e., no food consumption for 15 h during the light (inactive) phase per day for 5 weekdays, attenuated the outcome of diverse nutritional challenges in response to high-fat diet in mice. In the present study, we wanted to further test whether this TRF could restrict body weight gain in both juvenile and adult animals when fed a high-fat diet. Fifty male Sprague-Dawley rats at ages from 5 to 27 weeks were used. First, we found that freely fed rats with 60% fat diet gained weight significantly, which was associated with more calorie intake (particularly during light phase) than those fed standard food (7% fat). Secondly, we found that TRF restricted high-fat diet-induced weight gain in both groups of juvenile rats (5 and 13 weeks of age) compared to freely fed rats with high-fat diet, despite the same levels of 24 h-calorie intake during either weekdays or the weekend. Thirdly, we found that TRF did not restrict high-fat diet-induce weight gain in adult rats (27 weeks of age). Thus, we suggest that this special TRF regimen could be further tested in humans (particularly young adults) for the purpose of obesity prevention.

1. Introduction

According to World Health Organization's report, >13% of the world population are obese, which is a doubling over the last 35 years. Of the world's 7.2 billion people, 25% are overweight or obese, >50 million children at the age of 5 are obese, and 266 and 375 million men and woman are obese, respectively [1]. In Europe, the EU Action Plan on Childhood Obesity 2014–2020 outlines actions targeted to make it easier for children to reduce their calorie intake [2]. In order for children to have proper linear growth and development, one should consider how to design new diet regimens for the purpose of obesity prevention without causing malnutrition.

Circadian rhythms play an important role in the regulation of metabolism to optimize energy use and storage. Both rodent and human studies have demonstrated that restricting food intake to the active phase (nighttime in rodents and daytime in humans) limits metabolic disturbances induced by high-energy diets, while eating during the inactive/sleep phase (daytime in rodents and nighttime in humans) leads to a worse metabolic outcome [3–8]. Hence, abolishment of eating during the inactive/sleep phase should be an ideal target for obesity prevention and treatment.

Animal research using different paradigms has often been performed to characterize the effects of timing of food intake on metabolic profiles in order to obtain the evidence to support a "best time" not to eat. Previous studies have shown that a high-fat diet altered daily feeding rhythm by increasing feeding during the inactive phase [9,10]. Indeed, mice fed a high-fat diet during inactive phase gained more weight than mice fed the same diet during the active phase [11]. Both animal study using male Zucker rats and pilot clinical study in 8 obese patients showed beneficial effects of time-restricted feeding (TRF) as an anti-obesity strategy [5,7]. It should be noticed that most animal studies of TRF were conducted in adult, but not juvenile rodents.

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Recently, Chaix et al. introduced a special weekly schedule of TRF regimen that allows only 9–12 h/day access to food for 5 days (i.e., during the weekdays), but free access to food during the weekend. Based on their results using mouse models, they suggested that this TRF regimen can be a preventative as well as therapeutic intervention against obesity [4]. This TRF regimen sounds more adaptable to people's lifestyles than current regimens including the so-called 5:2 diet and daily calorie restriction [12]. Thus, it has been particularly highlighted in *Science* as "You are not just what, but when you eat" [13].

In the study by Chaix et al., there was, however, no data showing why calorie intake during inactive phase was the target, and whether this specific TRF could prevent young animals from developing obesity under high-fat diet. Further, the method of determining food intake by Chaix et al. was performed by manually monitoring the food intake on a weekly basis.

In the present study, we wanted to expand these previous studies by analyzing the feeding rhythm and metabolic measurements in more detail (e.g., number of meals, meal size, intermeal interval, calorie intake, and energy expenditure) using Comprehensive Laboratory Animal Monitoring System (CLAMS) animals [14]. We used rats and not mice, because CLAMS is performed much more precisely in rats than in mice. The aims of the present study were; 1) to demonstrate that calorie intake during light (inactive) phase was an ideal target, particularly during the course of high-fat diet; 2) to examine whether this special TRF regimen might restrict the weight gain in young animals when fed a high-fat diet; and 3) to examine whether this TRF regimen might be used as a therapeutic intervention in older obese rats when fed high-fat diet.

2. Methods

2.1. Animals and high-fat diet

Rats (Sprague-Dawley, four weeks old, male) were purchased from Taconic (Ejby, Denmark). The diet-induced obese (DIO) rats were put on a 50:50 high-fat diet and normal diet for two weeks (from 5 weeks of age) before placed on 100% high-fat diet until the end of study [15]. The normal diet (ND) rats were kept on normal diet during the entire study. All animals were housed three-four together in individually ventilated cages on wood chip bedding with a 12 h light/dark cycle, room temperature of 22 °C and 40–60% relative humidity. The standard housing conditions were specific pathogen free and in agreement with FELASA (Federation of European Laboratory Animal Science Association) recommendations. Throughout the experiment, all animals had free access to tap water and food regardless of being in metabolic or Makrolon cages. The high-fat diet (5.24 kcal/g metabolizable energy) (D12492) was purchased from Research Diets Inc. (New Brunswick, NJ, USA), and normal diet (7% fat, 2.57 kcal/g metabolizable energy) (RM1 811004) was purchased from Scanbur BK AS (Sweden). Body weight was measured every week from arrival until euthanization. Body composition analysis to ensure obesity was performed using dual energy X-ray absorptiometry (DXA), while CLAMS was used to analyze eating behavior in obese and non-obese age-matched controls. Animal experiments were performed according to the guidelines for the design and statistical analysis of experiments using laboratory animals after being approved by the Norwegian National Animal Research Authority (Forsøksdyrutvalget, FDU).

2.2. Time-restricted feeding

The rats placed on time-restricted feeding (TRF) regimen had freely access to food for 9 h per day (21:00 to 06:00) during the dark phase (19:00–07:00), for 5 weekdays. During these weekdays, food was manually removed at 06:00 to ensure no food consumption for subsequent 15 h. However, during the weekend (2 days), rats were allowed to have freely access to food for 24 h per day.

2.3. Experimental design

Fifty rats were used in three experiments (Fig. 1). Experiment no. 1 was performed to obtain basic information. Two groups of age-matched rats (5–35 weeks of age) were given either high-fat diet (HFD) to induce obesity (DIO) (n = 12) or were fed normal diet (ND) (n = 8). In experiment no. 2, we wanted to test whether TRF could prevent DIO. TRF was applied in juvenile rats fed HFD either starting at 5 weeks of age for 12 weeks (n = 6) or starting at 13 weeks of age for 4 weeks (n = 6) vs. time-matched controls fed HFD ad libitum (n = 6). Male Sprague-Dawley rats at 4–5 weeks of age correspond to pre-adolescent in humans, as they would reach sexual maturation at 6 weeks [16]. In experiment no. 3, we wanted to test whether TRF could induce body weight loss in adult DIO rats. TRF was started at 18 weeks of age and lasted for 9 weeks (n = 12). The effect of TRF was assessed in animals acting as their own control. The studies reported here were conducted over a 3-year period in the same state-of-the-art facility, under controlled conditions and using animals sourced from a single supplier.

2.4. Measurements of energy balance

The animals were acclimatized to the Comprehensive Laboratory Animal Monitoring System (CLAMS; Columbus Instruments International, Columbus, OH USA) for 24 h before data collection. CLAMS analysis was performed in the following experimental groups: ND and DIO rats at 35 weeks of age (experiment no. 1), HFD juvenile rats with and without TRF at 7 weeks of age (experiment no. 2) and, adult DIO rats before and during TRF (17 weeks and 24 weeks of age, respectively) (experiment no. 3). We did not perform CLAMS analysis of the second TRF group (13 weeks, experiment no. 2), because we assumed it would be the same as the first TRF group (5 weeks, experiment no. 2). At data collection, the animals were kept in CLAMS for 72 h and data from the last 48 h were used for analysis. Animals were placed in CLAMS with access to expanded high-fat diet or normal diet, and tap water. This system is composed of a four-chamber open circuit indirect calorimeter designed for continuous monitoring of individual animals.

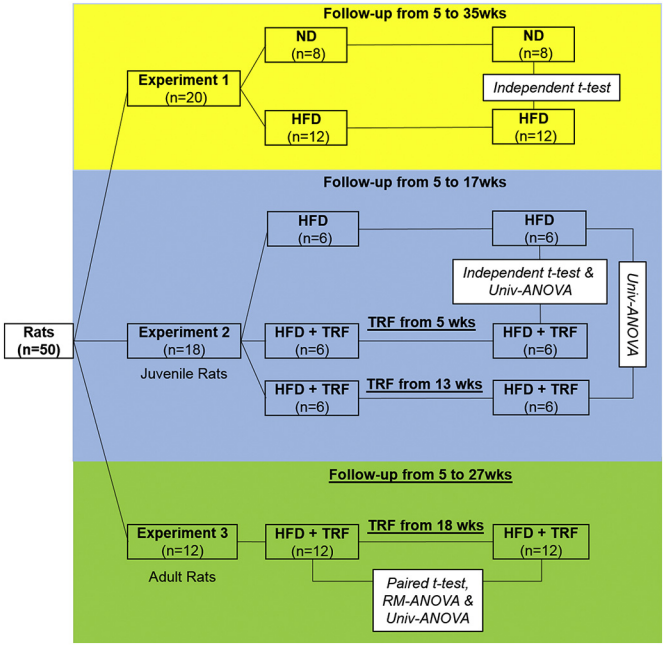

Fig. 1. Study design. ND: normal diet; HFD: high-fat diet; TRF: time-restricted feeding, i,e., no food consumption for 15 h during the light (inactive) phase per day for 5 weekdays; Univ-ANOVA: univariate analysis of variance; RM-ANOV: repeated measures analysis of variance.