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ORIGINAL ARTICLE

Brown adipose tissue transplantation ameliorates male fertility impairment caused by diet-induced obesity

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Summary Populations with obesity or overweight have a high incidence of infertility. We hypothesised that brown adipose tissue (BAT) transplantation can attenuate the impairment of male fertility caused by diet-induced obesity. BATs were transplanted from male donor mice into age and sex matched recipient mice fed high-fat diets (HFD). Sperm motility experiment was conducted after surgical procedure. X-ray computed tomography scanning, biochemical assay, real-time PCR and western blot analysis were performed. BAT transplantation reduced body fat and epididymal fat mass, as well as triglycerides (TG) content in testis and epididymis and total cholesterol (TCHO) contents in epididymis compared with the HFD group. Sperm motility and progressiveness were recovered and mRNA and protein levels of genes related to sperm motility such as cullin 3 (Cul3), peroxisome proliferator activated receptor alpha (PPARα) and its down-stream genes were significantly down-regulated post BAT transplantation. BAT transplantation partially ameliorated impairment of male fertility caused by diet-induced obesity.

Introduction

Obesity has increased dramatically worldwide over the past 20—30 years. According to the report from WHO, approximately 1.6 billion adults were

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classed as being overweight and 400 million adults were obese in worldwide in 2005 [1]. Statisticians had predicted that, by 2015, approximately 2.3 billion adults would be overweight and 700 million would be obese [1]. The worldwide epidemic of obesity has shown numerous negative effects on health; it has increased the risk of developing chronic diseases such as diabetes mellitus, hypertension, cardiovascular diseases and stroke [2]. Until recently, scientists begin to realise that populations with obesity or overweight exhibit a high incidence of infertility [3—7]. There are some reports indicating that paternal obesity may negatively affect basic sperm parameters such as concentration and motility [7—9]. However, the relationship between obesity and male fertility need to be further elucidated.

Recently, studies found that brown adipose tissue (BAT) transplantation can improve whole-body energy metabolism, regulates glucose homeostasis and insulin sensitivity [10—12]. BAT is a mitochondrial rich tissue that uses glucose and fatty acids as a fuel rather than the traditional adipose tissue as a lipid storage tissue. BAT regulates thermogenesis upon environmental stresses to maintain energy balance and protect the organism from hypothermia [13]. BAT thermogenesis is achieved by dissipating heat produced from fatty acid oxidation. Weight loss can be achieved by increasing energy expenditure through activating BAT [14]. The previous study has shown that BAT transplantation can regulate the whole-body energy metabolism, significantly decreased body weight and improved glucose metabolism and insulin sensitivity, in both normal diet-fed and high fat diet-fed mice [15]. In this study, we aim to investigate whether BAT transplantation can also affect the male fertility by diet-induced obesity.

Materials and methods

Animals breeding and diet

Three weeks old male C57BL/6J mice (Vital River Laboratories, Beijing, China) were maintained in a SPF grade facility, on a standard 12-h light/12-h dark cycle. Twenty four mice were randomly divided into two groups according to the original body weight using the software SPSS 17.0 (SPSS, Inc., Chicago, IL). Normal diet group (ND) as control ($n = 8$) were fed with a standard mouse diet (10% kcal from fat) (Research Diets Inc.), high fat diet group ($n = 16$) were fed with a high-fat diet (60% kcal from fat) (Research Diets Inc.). Body weights of mice fed with a high-fat diet for 8 weeks were increased by 24% compared to ND group. Then, these obese mice were equally divided into two subgroups, one group for brown adipose tissue transplantation (BAT + HFD) and another group for HFD sham group (HFD). Two subgroups continued to feed with high-fat diet after operation until the end of experiment. All animal care and experimentation were conducted in accordance with the National Research Council publication Guide for Care and Use of Laboratory Animals [16].

Isolation of donor tissue and transplantation

The transplanted brown adipose tissue (BAT) was obtained from intrascapular region from the donor mice sacrificed by cervical dislocation, and rinsed in pre-warmed 37 °C PBS before transplantation. All the operations should be manipulated in a sterile laminar flow hood. Transplantation surgeries were performed under general anesthesia with avertin (250 mg/kg i.p.). For age and sex matched recipient mouse, about 0.15 g donor BAT from intrascapular region was transplanted into 8 week old C57BL/6J mice, respectively. A small (1—2 mm) incision were made by scissors underneath the skin of the dorsal body surface, a subcutaneous pocket was made by blunt tweezers. Donor tissue was introduced into the pocket with Dumont forceps and the incision was closed by wound closure. The others mice were operated a sham operation. The post-operation mice were warmed up under a warming lamp until recovery, and post-operation anti-inflammation was provided with sodium penicillin (100,000 U/kg/d i.m.) for about one week. After the operation, all of mice were bred with corresponding diet for each group for another 14 weeks.

X-ray computed tomography scanning

After 14 weeks, the body fat composition was measured by an X-ray computed tomography (CT) system for small experimental animals with a mouse mode (Latheta LCT-200, Hitachi Aloka Medical, Ltd., Tokyo, Japan). The visceral and subcutaneous fat volumes computed automatically were compared with those after the radiologist's adjustments. Energy from −140.0 to 350.0 was defined as lean, and from −550.0 to 140.0 was defined as fat.

Sperm motility and progressive analysis

After X-ray CT scanning, the males were sacrificed for sperm motility and progressive analysis and samples collection for biochemistry analysis, real time PCR and western blot. The parameters of sperm motility and progressive were measured by computer assisted sperm analysis (CASA) system

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