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Obesity-induced oxidative stress, accelerated functional decline with age and increased mortality in mice

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A B S T R A C T

Obesity is a serious chronic disease that increases the risk of numerous co-morbidities including metabolic syndrome, cardiovascular disease and cancer as well as increases risk of mortality, leading some to suggest this condition represents accelerated aging. Obesity is associated with significant increases in oxidative stress *in vivo* and, despite the well-explored relationship between oxidative stress and aging, the role this plays in the increased mortality of obese subjects remains an unanswered question. Here, we addressed this by undertaking a comprehensive, longitudinal study of a group of high fat-fed obese mice and assessed both their changes in oxidative stress and in their performance in physiological assays known to decline with aging. In female C57BL/6J mice fed a high-fat diet starting in adulthood, mortality was significantly increased as was oxidative damage *in vivo*. High fat-feeding significantly accelerated the decline in performance in several assays, including activity, gait, and rotarod. However, we also found that obesity had little effect on other markers of function and actually improved performance in grip strength, a marker of muscular function. Together, this first comprehensive assessment of longitudinal, functional changes in high fat-fed mice suggests that obesity may induce segmental acceleration of some of the aging process.

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Introduction

The prevalence of obesity among all age groups in the US population has risen dramatically over the last few decades due in part to increased sedentary behavior and availability of high calorie food choices [1,2]. Without intervention, a large proportion of this population will be obese (defined as BMI $\geqslant$30) for a significant proportion of their lives. That is, people are living longer with obesity and are thus subject to increased incidences of the numerous co-morbidities associated with this condition. Obese subjects are at an elevated risk of early mortality, likely due to dramatic increases in the occurrence and severity of chronic illnesses such as cardiovascular disease, diabetes, and cancer among this group [3–5]. Interestingly, the spectrum of diseases that are exacerbated by obesity are relatively similar to those that increase in prevalence with normal aging. Further, the deterioration and pathology of organs that occurs with chronic obesity is in many ways similar to that which occurs in normal aging leading some to suggest that chronic obesity accelerates the aging process.

There is substantial evidence that elevated oxidative stress mediates the progression of many of the comorbidities associated with obesity. The expansion of adipose tissue is linked with an increased production of reactive oxygen species (ROS)[1] in both human and rodent models through various mechanisms [6,7]. Moreover, the production and secretion of inflammatory adipokines from adipose tissue under metabolic stress promotes a positive feedback loop further exacerbating oxidative stress both in this tissue and throughout the body [8,9]. The accumulation of oxidative stress is

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[1] *Abbreviations used:* ROS, reactive oxygen species; QMRi, Quantitative Magnetic Resonance imaging; 4-HNE, 4-hydroxynonenal; RQ, respiratory quotient; RMR, resting metabolic rate.

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an early event in the pathology of obesity which precedes, and likely drives, the development of insulin resistance and diabetes [6,10]. This hypothesis is directly supported by studies that show reducing oxidative stress, either genetically or pharmacologically, does prevent metabolic dysfunction induced by high fat feeding in mice [11–13]. This condition of high metabolic and oxidative stress is also thought to drive the prevalence and incidence of other comorbidities of obesity including cardiovascular disease and cancer [14].

Despite the well-examined relationship between aging and oxidative stress, it is not clear whether the high-levels of oxidative stress caused by obesity could contribute to an acceleration of the aging process. A limited number of studies have shown that obesity in mice, whether due to genetic mutation or high fat feeding, are relatively short-lived compared to lean mice [15–18]. However, there remains a clear need to address both the causes and consequences of these outcomes. We addressed this question by undertaking a comprehensive, longitudinal study of a group of high fat-fed obese mice and assessed their performance in assays designed to measure several physiological functions known to decline with aging. By assessing a broad-range of functional assays, we can more clearly address whether obesity fundamentally alters the rate of aging across a wide spectrum of tissue and organ systems or, alternatively, whether obesity shortens lifespan due to the increased incidence of a discrete spectrum of diseases. In accordance with previous reports, high fat-fed female C57BL/6J mice showed a significant reduction in lifespan and increased levels of oxidative stress/damage *in vivo*. We found that both diet and age affected metabolism, muscular function, and coordination. Further, we identified that high fat-fed mice displayed evidence for accelerated decline in function after parsing out independent effects of increased body weight in these assays. Together, our data support the notion that the increase in mortality associated with obesity may be due to an accelerated aging rate of some physiological systems.

Methods

Mice

Female C57BL/6J mice bred in-house were used for all studies. All animal studies were conducted under SPF conditions in a facility maintained at a temperature of 22–25 °C under a 12 h light cycle (06:00 on–18:00 off). From weaning until 8 months of age, mice were maintained on a standard rodent chow based on the NIH-31 open source (Harlan Teklad, Madison, WI). At 8 months of age, mice were randomly assigned to new cages at a density of 5 mice/cage. Each cage was randomly assigned to be fed either the standard rodent chow or a defined, high fat diet. Mice were checked daily and provided food and water *ad libitum* for the remainder of their natural life. Sample sizes at the beginning of experiments were $n = 15$ on chow and $n = 40$ on high fat diet. All animal studies were performed in accordance with the Institutional Animal Care and Use Committee (IACUC) at the University of Texas Health Science Center at San Antonio.

High fat diet

The high fat diet (catalog ID 58V8 or D12451) used in this study was a defined diet containing 45% total kCal from fat (or 23.6% of total weight) and was purchased from Purina/Test Diet (St. Louis, MO). The primary fat sources of this diet was lard (20.7% of total weight) and soybean oil (2.9% of total weight). Monthly, average food consumption over a one week period was determined per cage by measurement of remaining food and food waste.

Body composition

Body weight and composition were measured bi-weekly in non-anesthetized mice by Quantitative Magnetic Resonance imaging (QMRi) using an EchoMRI 3-in-1 composition analyzer (Echo Medical Systems, Houston, TX).

Measurement of oxidative stress and inflammation

F_2-isoprostane content was performed by chromatography–mass spectrometry as previously described by our group [12]. Protein-bound 4-HNE was measured by immunoblot using a primary anti-4 HNE antibody (Abcam, Cambridge, MA). Flash frozen liver or skeletal muscle samples were homogenized in RIPA buffer and separated by SDS–PAGE. After transfer to PVDF membrane and immunoblot, samples were visualized using ECL and quantified using ImageJ. Total superoxide and glutathione peroxidase activity were determined using colorimetric assays as per instructions of manufacturer (Cayman Chemical, Ann Arbor, MI). IL-6 and TNFα were measured in plasma samples by ELISA using manufacturer's instructions.

Glucose metabolism

Glucose tolerance tests were performed in mice fasted overnight and injected intraperitoneally with glucose (in saline) at a dose of 1.5 mg kg^{-1} body weight. Blood glucose levels were measured using hand-held glucometer (One Touch Ultra). Insulin levels were measured in previously-frozen plasma samples by ELISA per manufacturer's instructions (Crystal Chem, Downer's Grove, IL).

Respirometry

Resting metabolic rate, oxygen consumption, and carbon dioxide production, were measured for a period of 24 h using a MARS indirect calorimetry system (Sable Systems International, Las Vegas, NV). Mice were individually housed with TEK-Fresh cellulose bedding and provided food and water *ad libitum* during metabolic measures. Animals were habituated to the cage and respirometry system for 12 h prior to testing.

Spontaneous activity

Mice were housed individually in clear, plexiglass ($40.6 \times 22.9 \times 14.0$ cm) cages surrounded by a 2.5-cm grid of infrared sensors to record spontaneous activity in the *x*, *y*, and *z* plane with normal access to food and water. Each motion detected by these sensors is recorded as a beam break. Mice are acclimated to cages for the first 12 h, following which beam breaks are measured for 24 h, which includes one light and one dark phase cycle.

Gait analysis

Mice were tested on the TreadScan (Clever Sys, Reston, VA) apparatus starting at a treadmill speed of 12 cm/s. Belt speed is adjusted until mice maintain a constant walking speed for 5 min and this speed was used for all subsequent assays. Using a high-speed digital camera to record the reflected images of the footpads at 80 frames/s, these images are used to assess more than 40 parameters of gait using mouse-specific algorithms included in the TreadScan software program.

Grip strength

Fore- and hind-limb grip strength were measured using a Grip Strength Meter with mesh grid pull bar (Columbus Instruments

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